PEDIATRIC CLINICS OF NORTH AMERICA

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Symposium on Fluid and Electrolyte Problems

Lewis A. Barness, M.D.
Consulting Editor

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CONTRIBUTORS

FEBRUARY ISSUE

WOLFGANG ANKE, M.D. Chief Resident in Pediatrics, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

GIULIO J. BARBERO, M.D. Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine; Associate Physician and Member of Research Staff, Children's Hospital, Philadelphia, Pennsylvania.

LEWIS A. BARNESS, M.D. Associate Professor of Pediatrics, University of Pennsylvania School of Medicine; Acting Chief of Pediatrics, Hospital of the University of Pennsylvania; Chief of Pediatrics, Philadelphia General Hospital; Assistant Visiting Physician, Children's Hospital, Philadelphia, Pennsylvania.

WILLIAM H. BERGSTROM, M.D. Associate Professor of Pediatrics, State University of New York, Upstate Medical Center; Associate Attending Pediatrician, Syracuse Memorial Hospital, Syracuse, New York.

ALFRED M. BONGIOVANNI, M.D., F.A.A.P. Associate Professor of Pediatrics, University of Pennsylvania School of Medicine; Director, Department of Endocrinology, Children's Hospital, Philadelphia, Pennsylvania.

JOHN D. BRIDGERS, M.D. Associate in Pediatrics, University of Pennsylvania School of Medicine; Director of Clinics, Children's Hospital, Philadelphia, Pennsylvania.

SAUL W. BRUSILOW, M.D. Postdoctoral Research Fellow of the National Foundation for Infantile Paralysis, Johns Hopkins University School of Medicine, Baltimore, Maryland.

ELEANOR COLLE, M.D. Assistant Professor of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota.

ROBERT E. COOKE, M.D. Professor of Pediatrics, Johns Hopkins University School of Medicine; Pediatrician-in-Chief, Johns Hopkins Hospital; Director, Harriet Lane Home for Invalid Children, Baltimore, Maryland.

DAVID CORNFELD, M.D. Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine; Director of Pediatric Clinic, Hospital of University of Pennsylvania, Philadelphia, Pennsylvania.

JOHN D. CRAWFORD, M.D. Assistant Professor of Pediatrics, Harvard Medical School; Physician to Children's Medical Service, Massachusetts General Hospital, Boston, Massachusetts.

DANIEL C. DARROW, M.D., F.A.A.P. Professor of Pediatrics, University of Kansas Medical School; Professor of Pediatrics, Children's Mercy Hospital, Kansas City, Missouri.

PHILIP R. DODGE, M.D. Instructor in Pediatrics, Harvard Medical School; Assistant Neurologist, Massachusetts General Hospital, Boston, Massachusetts.

THOMAS J. EGAN, M.D., C.M. Assistant Instructor in Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

MARY ALLEN ENGLE, M.D., F.A.C.P., F.C.C.P., F.A.A.P. Assistant Professor of Pediatrics, Cornell University Medical College; Assistant Attending Pediatrician, The New York Hospital, New York City.

LAURENCE FINBERG, M.D., F.A.A.P. Assistant Professor of Pediatrics, Johns Hopkins University School of Medicine; Assistant Chief Pediatrician, Baltimore City Hospital, Baltimore, Maryland.

LYTT I. GARDNER, M.D., F.A.A.P. Professor of Pediatrics, State University of New York, Upstate Medical Center; Attending Pediatrician, Syracuse Memorial Hospital, Syracuse, New York.

ROBERT E. GREENBERG, M.D. Research Fellow in Pediatric Endocrinology, State University of New York, Upstate Medical Center, Syracuse, New York.

GEORGE M. GUEST, M.D., F.A.A.P. Professor of Research Pediatrics, University of Cincinnati College of Medicine; Attending Pediatrician, Children's Hospital and Cincinnati General Hospital, Cincinnati, Ohio.

HAROLD E. HARRISON, M.D. Associate Professor of Pediatrics, Johns Hopkins University School of Medicine; Pediatrician-in-Chief, Baltimore City Hospital, Baltimore, Maryland.

MALCOLM A. HOLLIDAY, M.D., F.A.A.P. Assistant Professor of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

ROBERT KAYE, M.D. Associate Professor of Pediatrics, University of Pennsylvania School of Medicine; Director of Teaching, Children's Hospital, Philadelphia, Pennsylvania.

WILLIAM J. MELLMAN, M.D. Assistant Instructor of Pediatrics, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

JACK METCOFF, M.D., F.A.A.P. Professor of Pediatrics, Northwestern University Medical School; Chairman, Division of Pediatrics, Michael Reese Hospital, Chicago, Illinois.

FRANK A. OSKI, M.D. Interne, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

ELSA PROEHL PAULSEN, M.D. Postdoctoral Fellow, United States Public Health Service, Albert Einstein College of Medicine, New York City.

GERALD W. PESKIN, M.D. Associate in Surgery, Surgical Staff, Hospital of the University of Pennsylvania; Consultant, Veterans Hospital, Philadelphia, Pennsylvania.

DAVID M. PICOU, M.B., B.S. (U.C.W.I.) Research Fellow, Children's Hospital, Philadelphia, Pennsylvania.

HELEN SEIBERT REARDON, M.D., F.A.A.P. Assistant Professor of Pediatrics, Temple University School of Medicine; Attending Pediatrician, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.

MAARTEN S. SIBINGA, M.D. Instructor in Pediatrics, New York University Medical School; Lee Graub Research Fellow in Cystic Fibrosis Research and Member of Research Staff, Children's Hospital, Philadelphia, Pennsylvania.

WILLIAM M. WALLACE, M.D., F.A.A.P. Professor of Pediatrics, Western Reserve University School of Medicine; Director of Pediatrics, Babies and Children's Hospital, Cleveland, Ohio.

WILLIAM B. WEIL, Jr., M.D. Assistant Professor of Pediatrics, Western Reserve University School of Medicine; Associate Pediatrician, Babies and Children's Hospital, Cleveland, Ohio.

CLARK D. WEST, M.D. Associate Professor of Pediatrics, University of Cincinnati College of Medicine; Attending Pediatrician, Children's Hospital and Cincinnati General Hospital, Cincinnati, Ohio.

ROBERT W. WINTERS, M.D. Department of Biochemistry, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. Formerly Postdoctoral Fellow, National Foundation for Infantile Paralysis, University of North Carolina School of Medicine.

CHARLES C. WOLFERTH, M.D. Assistant Instructor in Surgery, and Fellow, Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

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SYMPOSIUM ON FLUID AND ELECTROLYTE PROBLEMS

FOREWORD

LEWIS A. BARNESS, M.D.

Consulting Editor

Reviews of fluid therapy, like water, are everywhere. Some are more comprehensible than others, and the tendency is to make them simpler as understanding becomes better. When Drs. James Gamble, Alan Butler, Daniel Darrow and George Guest were first discovering the 70 to 80 per cent place of fluid in the body, they were considered a breed apart and labelled "salt and water boys." The label is finally being dropped as more knowledge brings ready use of their principles of fluid therapy.

That pediatricians should be most interested of all physicians in exactness in fluid therapy arises from two basic causes. Pediatricians traditionally have been in the vanguard of scientific advances in medicine. Indeed, some even believe that pediatrics split off from internal medicine in order to develop science as well as art in medicine. Pediatricians were part mathematicians: thereby the sad tale of early pediatrics, with rigid formulas for babies, rigid schedules for babies and, finally, rigid babies.

A more valid reason for exactness in fluid therapy in children is that small changes in fluid intake, though negligible in an adult, may be disastrous in a small child with small total fluid volume. Thus the surgeon for an adult can easily say, "Hang up a bottle of glucose water," knowing that the entire bottle contains only 5 per cent of the adult's extracellular volume and that he can easily adjust for any small errors in salt and water. A baby, on the other hand, may have a total extracellular fluid volume not much greater than that same bottle and may have immature kidney and liver function; therefore fluid therapy must be much more clearly defined as to total volume, rate of infusion, and electrolyte and water content.

Fluid therapy of children is simple. Those who consider it complicated either have had too little experience or have a psychologic block about some formidable formulas. Unfortunately, in their desire to make fluid therapy universally applicable, some leaders in salt and water therapy have been seeking common denominators which are not so common in practice.

A few of these denominators are agreed on by all, and should be used by all physicians. First, regardless of how accurately fluids are calculated, the best evidence of proper fluid therapy is the patient. Therefore the patient should be carefully watched while fluids are being administered parenterally, and therapy should be adjusted according to the patient's response. Second, the best evidence of degree of hydration in a child is change of weight. Therefore all children receiving parenteral fluids should be weighed daily. Third, physicochemical responses of ions occur in proportion to their equivalents, and not according to gram weights. Therefore serum electrolytes and electrolytes administered should be in terms of milliequivalents (mEq.) or millimols (mM.), not milligrams (mg.). Those reared in an atmosphere of milligrams should convert to the more physiologic ionic milliequivalents:

$$\text{mEq. per liter} = \frac{\text{mg./100 ml.} \times 10}{\text{atomic wt.}} \times \text{valence}$$

For a few commonly used ions:

ION	VALENCE	ATOMIC WT.
Na	1	23
K	1	39
Cl	1	36
Ca	2	40

Volumes per cent of carbonic dioxide may be converted to millimeters per liter by dividing by 2.2. Further details are discussed by Dr. Bergstrom (p. 5*ff*.).

This is practically the end of the areas of common agreement in therapy. In this volume it will be noted that some authors prescribe fluids on the basis of weight of the patient; others on the basis of surface area; and still others according to the number of calories utilized. Obviously, none is satisfactory, or one system would be universally adopted. The problems involved with all these systems are clearly covered by Dr. Darrow in his clinic (p. 29*ff*.).

Whether salt should be expressed in terms of water in the body or water according to its salt content, each physician can decide. Drs. Metcoff and Crawford have used systems which contain both concepts. Sometimes it seems as if we must stand on our heads to appreciate the more physiologic concept of concentration of water. Dr. Holliday, how-

ever, who discusses the physiology of dehydration, uses the more conventional concept of concentration of salt.

Each of the authors of the section on Clinical Applications has apologized for "having to include some physiology" in his discussion—a real tribute to pediatricians. Therefore some duplication occurs. Fortunately, this makes for easier reading as each pathologic condition is discussed fully.

More information is included in some of the clinical articles than is indicated in the title. For example, Dr. Kaye includes new data on fat solutions as well as techniques of fluid administration through all portals. Dr. Cooke clearly gives concise information not only of diarrhea and vomiting, but also of tricks of fluid therapy; Drs. Guest and Wallace go far beyond simple fluid therapy; Dr. Gardner answers well the question of how fluid therapy differs in children with infection; and the various aspects of surgical fluids are covered in the two papers of Drs. Colle and Paulsen, and Wolferth and Peskin. Dr. Reardon not only discusses fluid therapy of infants, but also presents concepts which may alter treatment drastically in this very labile period. Dr. Harrison discusses the still-controversial problem of hyperelectrolytemia, and Dr. Cornfeld discusses a syndrome about which we are hearing less and less. Dr. Bongiovanni has recently written on the "Proper Use of Adrenal Hormonal Drugs," so that he quite aptly tells now what to do if the "hormonal drugs" are used improperly. Dr. Barbero discusses the theoretical as well as the practical aspects of fluid therapy in a troublesome respiratory disease which should be the battleground of fluid therapists; and Dr. Engle advises mainly against fluid therapy in the "fluid therapy of heart failure." Dr. Crawford's article is not only an admirable discussion of fluid therapy, but also an admirable presentation in humility. Dr. Winters covers the whole problem of salicylism, Dr. Oski mentions briefly some of the possibilities in chemistry at the bedside, and Dr. Mellman puts the reader in the proper psychologic approach for good bloodletting. The Editor would like to note also that Drs. John Reinhold and Howard Rawnsley of the Pepper Laboratories, Hospital of the University of Pennsylvania, gave aid and advice in the preparation of several of the papers included in this volume.

From this brief review it is noted that the minor ions are apparently not mentioned. This is not so. So far as data are available on such ions as magnesium and phosphate, these are included where applicable. As these ions attain their proper place in the minds of the "salt and water boys," a new review on fluid therapy will appear.

3600 Spruce Street
Philadelphia 4, Pennsylvania

TOTAL BODY WATER AND NORMAL ELECTROLYTE COMPOSITION

WILLIAM H. BERGSTROM, M.D.

The study of body composition is an ancient one, beginning with speculations about humors, phlegms and varicolored biles, progressing *pari passu* with the science of chemistry, and comprising finally a reasonably accurate quantitative description of the elements present in man and of their distribution in a system of several phases. This body of knowledge bears the same relation to biochemistry as anatomy does to physiology, and is similarly of interest and value chiefly so far as structure can be related to function, whether normal or abnormal. As physicians, we are interested in body composition as it indicates strengths and weaknesses—i.e., we must distinguish between those substances present in abundance and rarely vulnerable, such as calcium, phosphorus, magnesium and carbonate, and those in relatively short supply, such as water, chlorine, sodium and potassium, whose losses may rapidly lead to serious functional disturbances. As pediatricians we are further concerned with composition as a determinant of the characteristics of each successive age group from premature infant to adolescent. Also, we must consider the problem of growth in terms of daily increments of each element necessary for the maintenance of appropriate composition during periods of rapid change in body mass. Here again some substances are so abundant in the average diet and so readily assimilated that they are rarely or never implicated in growth failure—e.g., magnesium, potassium, sulfur, water and chlorine. Other constituents, such as iron, iodine and nitrogen, may be so deficient in the diet that normal growth is impossible. In still other instances the necessary daily increment for growth may so closely approximate the total dietary intake that disturbances in absorption readily jeopardize growth, as in the case of calcium and phosphorus.

Evidently, then, we should like to have available two sets of data, the one accurately describing composition of infants and of growing children at various ages, the other relating increments for optimal growth to average dietary intake throughout the postnatal growth period. Composition can have little clinical meaning when considered apart from the mechanisms which stabilize it, since constant exchange with the environment renders body content of any element at any time only the momentary resultant of intake and excretion. Renal regulation is treated in detail elsewhere in this symposium (p. 43*ff.*) and will be mentioned here only as its failure becomes a potential source of derangement of composition or growth arrest.

MATERIALS AND METHODS OF STUDY

Before we examine the available data, it may be of interest to consider the material and methods which have been used in their accumulation. This will enable us to appreciate the areas of relative certainty as well as the substantial gaps in our knowledge which unfortunately persist. Satisfactory normal human material for postmortem analysis has never been plentiful and has become scarcer in recent years. Collections of total body analyses assembled by Shohl,[31] Darrow and Hellerstein,[10] Wallace[33] and others uniformly show a relative abundance of data from the laboratories of Europe 30 to 70 years ago, but little work done within the past 25 years. In addition, subjects for analysis have been principally fetuses, newborn infants, and adults. Darrow and Hellerstein[10] conclude that "reasonably complete analysis of normal humans are limited to several newborn infants, one adult woman, and two men." This circumstance is particularly distressing to the student of growth, since a large hiatus is evident in the area of greatest interest, namely, that between birth and maturity.

The *gravimetric macromethods* used before World War I were fortunately accurate and satisfactory when used on the large samples available. An example of their validity is seen in the work of Gabriel,[15] whose detailed analyses of bone (carried out in 1894) have been repeatedly confirmed, but never significantly extended. However, a large amount of the older data is virtually useless for lack of adequate reference standards. Only relatively recently has it been shown by Lowry[24] and others that quantities of constituents must be referred to fat-free body weight or fat-free dry weight. Expression of content simply in terms of body weight does not permit comparison of data from different persons or even from the same person at different times, since variable fat content introduces an inert, largely mineral-free mass which has the effect of making the most carefully taken body weights meaningless.

In the modern era (since World War I) the *balance technique* has been put to good use by many investigators. Perhaps the most elegant

and detailed description of this approach is given by Reifenstein, Albright and Wells.[30] A more recent critique by Elkinton and Danowski[11] includes specific sample diets, methods of recording and calculating data, and appropriate warnings of common pitfalls. The performance of a "balance" requires accurate measurement of intake and excretion of the substance or substances to be studied during one or several arbitrarily chosen periods. Any measurable difference between intake and excretion is recorded as gain or loss. It would appear that increments for growth could be readily determined by performing such balance studies at appropriate intervals during infancy and childhood, and in fact a monumental collection of such data is available. However, several factors limit the usefulness of the balance technique. The technical difficulty of accurate collection of samples and the large number of analyses call for much scrupulous work by highly skilled personnel. The necessity for a carefully controlled diet and a restricted environment (the metabolism ward) sharply limit available subjects and may even vitiate the applicability of the data obtained to normal persons. Even when these obstacles are overcome and the surprisingly large financial resources needed are available, there remain systematic errors inherent in the balance method. These have been discussed by Gamble.[17] Essentially, errors in collection and in analysis of stools and urine tend to be cumulative rather than self-cancelling, with the result that larger retentions and smaller losses are described than actually occur. In addition, insensible losses of sodium, chloride and potassium are known to occur, but defy direct measurement except under unusually favorable conditions. For the same reason it is obvious that water and carbonate balances are feasible only for brief periods in elaborate apparatus. As a result, the greatest usefulness of the balance technique lies in the description of large and rapid changes in composition such as are seen during onset and recovery periods of acute illnesses and operative procedures.

The principle of measurement of an unknown mass or volume of a given substance by observation of the dilution of a known increment has long been applied to the study of various fluid phases. The volumes of blood, plasma, red cell mass, total body water and extracellular water have been determined, using such familiar substances as antipyrine, urea, Evans blue dye, bromide and variously tagged red cells in this fashion. One obvious advantage of the *dilution technique* is its application to living subjects. Data can be obtained much more readily than by the balance method, since the demands upon subject and investigator are relatively small. On the other hand, the interpretation of results is frequently difficult. For example, it is generally agreed that urea, antipyrine and deuterium are rapidly distributed throughout total body water. Inulin, thiosulfate and chloride, however, have different volumes of distribution, and the observed volume of inulin changes with time.

Correlation of the observed dilution volume with any physiologically significant phase may be difficult and uncertain. The general subject of phase definition by dilution techniques has been extensively discussed by Nichols and his associates.[28] As matters now stand, total body water may be measured with assurance, but extracellular water only with difficulty and often with controversial results. Since intracellular water cannot be measured directly, estimation depends on the difference between total and extracellular water. The uncertainties of the latter measurement are, therefore, reflected in any figure given for cell water.

Radioisotopes have enlarged the possibilities of the dilution technique. Whereas the substances mentioned above are limited in application to measurement of various fluid volumes, radioisotopes permit study of the masses of individual elements present in the body. The requirements for a useful isotope are availability, harmlessness (usually dependent on short half-life) and reasonably complete and rapid distribution paralleling that of the naturally occurring element under study.

Soon after radioisotopes became available for medical research, Kaltreider[23] found a large discrepancy between total body sodium and exchangeable sodium. This proved to be due to the substantial proportion (about one third) of total sodium present in the bone, as shown in 1936 by Harrison, Darrow and Yannet.[20] Bone sodium, according to the researches of Kaltreider and subsequent workers,[27] equilibrates with circulating radiosodium at two distinct rates, one rapid and one very slow. As a result of this circumstance, exchangeable sodium must be corrected by a suitable factor to give total sodium. The factor, unfortunately, is not only large, but also variable with age.

Exchangeable potassium likewise is less than total potassium, the ratio being 0.95. Here the explanation is less evident. Bone sequesters only a small amount of potassium,[3] and while the exchangeability of apatite potassium has not been studied, there is not enough of it altogether to account for the discrepancy.

The ratio $\frac{\text{Cl exch.}}{\text{Cl total}}$ is nearly unity. Radiochloride (or bromide) measurements, therefore, require no correction.

Table 1 presents data calculated from various sources, expressed in terms of fat-free body weight and permitting comparison between a newborn infant and an adult male, both hypothetical. In Table 2 average dietary intakes of several constituents are compared with total body content and with increments required for normal growth at various ages. Analyses of diet are those of Sherman as cited by Shohl.[31] The composition of milk is taken from Nelson,[26] as are growth rates. Body composition is calculated from various sources, the mathematical descriptions of growth given by Forbes[12] being used for water, sodium and potassium. Elements for which data are available will now be considered individually.

WATER

Total body water in Table 1 is that measured by deuterium. Extracellular water is defined by bromide. Intracellular water is found by

TABLE 1. *Chemical Constituents of Body*

CONSTITUENT	AMOUNT/KG. FAT-FREE WEIGHT	
	Infant	Adult
Water, total	780 cc.	650 cc.
Water, extracellular	390 cc.	275 cc.
Water, intracellular	390 cc.	375 cc.
Sodium, total	81 mEq.	61 mEq.
Sodium, exchangeable	77 mEq.	50 mEq.
Sodium, bone	9 mEq.	20 mEq.
Chloride	55 mEq.	37 mEq.
Potassium	41 mEq.	52 mEq.
Magnesium	8 mEq.	18 mEq.
Calcium	231 mM.	623 mM.
Phosphorus	183 mM.	374 mM.
Carbonate (HCO_3^- and $CO_3^=$)	38 mM.	75 mM.

TABLE 2. *Average Dietary Intakes Correlated with Total Body Content and Growth Requirements*

CONSTITUENT	AGE	DAILY INTAKE (cc. or mM./Kg.)	INTAKE: CONTENT	INTAKE: GROWTH REQUIREMENT
Water	6 mo.	100 cc.	0.15	33
	5 yr.	85 cc.	0.14	>100
	11 yr.	67 cc.	0.12	>100
	17 yr.	49 cc.	0.09	>100
Sodium	3 mo.	0.6–2.5 mM.	0.01–0.04	1.3–5.0
	6 mo.	0.6–2.5 mM.	0.01–0.04	4–15
	1 yr.	2.8 mM.	0.05	32
	5 yr.	2.0 mM.	0.04	>100
	11 yr.	2.0 mM.	0.04	>100
	17 yr.	2.5 mM.	0.05	>100
Potassium	3 mo.	1–4 mM.	0.10	14
	6 mo.	1–4 mM.	0.12	40
	1 yr.	5 mM.	0.11	84
	5 yr.	2.5 mM.	0.06	>100
	11 yr.	2.0 mM.	0.05	>100
	17 yr.	1.5 mM.	0.03	>100
Calcium	6 mo.	4 mM.	0.02	6
	1 yr.	3 mM.	0.02	10
	2 yr.	2.3 mM.	<0.01	16
	3 yr.	2.0 mM.	<0.01	20
	4 yr.	2.0 mM.	<0.01	15
	6 yr.	1.5 mM.	<0.01	13
	8 yr.	1.2 mM.	<0.01	9
	10 yr.	1.0 mM.	<0.01	8
	12 yr.	1.0 mM.	<0.01	6
	14 yr.	0.7 mM.	<0.01	6

difference. The first obvious contrast between infant and adult is the higher water content of the former. The difference, 130 cc. per kilogram, is due almost entirely to the larger extracellular component of the newborn. Cell water is nearly identical (390 vs. 375 cc.—a difference of less than 5 per cent, which lies well within the error of measurement). Premature infants, not tabulated, are known to be even more dilute, or, by adult standards, edematous. The relative excess of water in the infant confers little security against dehydration, however, since Table 2 shows that the daily turnover is equal to 15 per cent of the total body content, as compared to 9 per cent in the adult. This circumstance, according to Gamble,[16] reflects a higher metabolic rate in proportion to weight, necessitating greater insensible and renal water expenditures. The unique susceptibility of the infant to dehydration is, therefore, determined by functional rather than compositional factors. The water requirement for normal growth is equal to 20 per cent of the intake at 3 months, decreasing rapidly thereafter until at 1 year it represents less than 1 per cent of the intake. It is obvious that water deprivation threatens survival rather than growth. There is no water storage or reservoir in the body, and the limits of variability in hydration consistent with health are fairly narrow. A loss of 10 per cent of body weight as water (equal to 16 per cent of body water, or a single day's turnover in infancy and early childhood) results in severe clinical dehydration and an equal excess in edema. Total body water, as measured by deuterium, is rapidly and completely accessible, the final volume of distribution of the tracer being reached within five hours. This implies that changes in osmotic concentration in the extracellular phase are rapidly reflected in cell water. The converse may also be true. Hypotonicity observed in tuberculosis and other infections may, according to Harrison and his associates,[19] be due to alterations in the osmotic activity of intracellular substances.

SODIUM

Total sodium in Table 1 was calculated from Forbes' exchangeable sodium data[12] by adding the quantity of nonexchangeable bone sodium estimated to be present. The latter figure was obtained by combining the sodium-calcium ratio for young and adult animals, the total skeletal calcium for infants and adults given by Shohl, and the proportions of exchangeable to total bone sodium found by Forbes[13] and Munro.[25] The use of such a mélange of animal and human data, though undesirable, is supported by the essential identity in composition of bones of various species. It is technically difficult to analyze for sodium in the presence of large quantities of calcium, and many of the available total body analyses for sodium are accordingly suspect.

A higher proportion of sodium in the infant is predictable from his relatively greater extracellular water content.

It is interesting to compare exchangeable with total sodium in each age group. In infancy exchangeable sodium comprises 95 per cent of total sodium; in the adult, 82 per cent. Bone equals about 15 per cent and 21 per cent of the respective fat-free weights, according to Shohl. The degree of mineralization of bone increases by a factor of 9.5/5.1 during the growth period, and the proportion of sodium to calcium increases in the ratio of 22/14. The relative amount of sodium in bone in the adult is, therefore,

$$\frac{21}{15} \times \frac{9.5}{5.1} \times \frac{22}{14}$$

four times that present in the infant. Simply stated, about 10 per cent of the infant's total sodium is combined with bone mineral, and of this fraction about half equilibrates rapidly with circulating radiosodium. In the adult one third of the total sodium is in bone, and one third of bone sodium is readily exchangeable. Experimentally produced metabolic acidosis of various sorts regularly causes a decrease in bone sodium, the amount so mobilized being approximately equal to that exchangeable with radiosodium.[3] Corresponding quantities of carbonate are liberated,[4] with the result that a variable fraction of bone sodium acts as "buffer base."

Intracellular water contains approximately 10 mEq. of sodium per liter. Exchangeability is apparently complete in this phase. Numerous investigators have found that intracellular sodium decreases in acidosis, about 85 per cent being lost within 48 hours.[7]

With the above information we can calculate the total buffer sodium of the infant as follows:

1. Extracellular buffer base = HCO_3^- = 21 mEq./L. × 0.390 = 8 mEq./kg.
2. Bone buffer sodium = 9 mEq./kg. (total) × 0.5 (fraction exch.) = 5 mEq./kg.
3. Intracellular buffer sodium = 10 mEq./L. × 0.390 = 4 mEq./kg.

Total 17 mEq./kg.

For the adult

1. Extracellular buffer base = HCO_3^- = 23 mEq./L. × 0.275 = 6 mEq./kg.
2. Bone buffer sodium = 20 mEq. × ⅓ (fraction exch.) = 7 mEq./kg.
3. Intracellular buffer sodium = 10 mEq./L. × 0.395 = 4 mEq./kg.

Total 17 mEq./kg.

Although the newborn has 30 per cent more sodium than the adult, buffer sodium available in acidosis is equal in the two age groups considered. The proportion sodium intake/exchangeable sodium content calculated in Table 2 is constant at all ages from infancy to adult life, amounting to 4 to 5 per cent. These figures are based on average dietary sodium, which beyond infancy is largely a function of the amount of

salt used in cooking and at the table. Salt use varies widely according to geographic region, season and cultural dietary patterns. The table, therefore, is only roughly applicable to any given subject except in the first few months of life, when diet is reasonably uniform. Here two groups of babies must be considered. The breast-fed infant at 3 months has an approximate intake of 0.6 mEq. per kilogram as compared to a growth requirement of 0.45 mEq. per kilogram. The ratio intake/exchangeable content is 1 per cent. The formula-fed baby, however, has an intake/requirement ratio of 5 and an intake/content ratio of 4 per cent. At first glance the greater sodium intake of artificially fed babies might appear to be a safety factor in the event of acidosis. This, however, is fallacious for two reasons. First, the higher sodium content of formula is associated with an equally elevated chloride and sulfate concentration—i.e., the cation load is triple or quadruple that of breast milk. Also, disturbances causing acidosis in this age group (principally diarrhea) regularly curtail or eliminate the usual dietary intake.

It is logical to consider whether excess dietary sodium can be stored in bone as potentially valuable buffer base. Bone sodium can be increased or decreased experimentally by drastic changes in intake. The maximum increase reported after very large loads is 8 per cent.[29] According to Table 1, this degree of change in bone would not significantly enhance total body buffer sodium in infancy. While long-term experiments bearing on this question have not been reported, it seems unlikely that extra dietary sodium has any effect beyond increasing renal solute load.

When cardiac or renal disease causes edema in young patients, the question of salt restriction may arise. Table 2 shows that after the first year the ratio of intake to growth requirement is so large that even a thirtyfold reduction in dietary sodium need not jeopardize growth. Up to six months a fivefold to fifteenfold reduction may cause slowing or cessation of growth. This may result from the use of sodium-free milk or from repeated paracenteses (each of which removes 120 to 140 mEq. of sodium per liter of ascitic fluid withdrawn). Obviously the clinical situation may still demand sodium restriction; growth arrest should, however, be a calculated risk rather than an unpleasant surprise.

CHLORIDE

Since analyses for chlorine are relatively simple and precise, information about its quantity and distribution in the body is readily available. Very small amounts may be present in total intracellular water, perhaps reflecting the inclusion of erythrocyte water, known to contain chloride in substantial concentration. Some degree of binding by collagen has been suggested to account for the fact that the "chloride space" of tendon and skin exceeds the total water content. After corrections for

collagen and erythrocytes, the remainder of total body chloride may be assigned to extracellular water. Darrow has pointed out that intracellular chloride cannot be excluded in disease on the basis of data garnered chiefly from normal subjects.[10]

Chlorine is not included in Table 2 since its dietary distribution and variable requirement for growth so closely parallel those for sodium that little is to be gained by a detailed separate consideration. There is no chloride reservoir.

POTASSIUM

Potassium content is essentially a function of muscle mass, since this element is chiefly intracellular, and muscle comprises most of the cell water of the body. Accordingly, the adult has more potassium than the infant. Bone probably contains about 5 per cent of the total potassium in adults, but technical difficulties are such that the figure is only a rough estimate. While there is evidence that bone potassium changes in acidosis as does sodium, the amounts involved are too small for accurate definition or practical significance. The ratio of sodium to potassium in cell water, normally 10/155, varies directly with plasma pH; conversely, experimental alterations of the ratio predictably influence plasma bicarbonate. This interesting relationship, discovered by Darrow and his co-workers,[9] has been extensively discussed by Cooke[6] in terms of renal tubular function. Though an elegant example of the influence of composition on function is thus provided, the argument is too complex for inclusion here.

Table 2 shows that potassium intake greatly exceeds the growth requirement except in early infancy. Even here it is so difficult to dissociate potassium from nitrogen and caloric content that only brief dietary deficits are conceivable. A contrast with sodium is evident, since the latter can be readily restricted. Two factors jeopardize potassium content during the common gastrointestinal disorders of infancy. One is the high potassium content of diarrheal stools; losses by this route may equal 10 to 15 per cent of total body content daily. The second is relatively slow and incomplete renal conservation as compared to the prompter defense of sodium. As the disease progresses, starvation and consequent tissue destruction supply large amounts of potassium in released cell water. As Darrow showed long ago,[8] critical potassium shortage may not become apparent until rehydration is accomplished without appropriate provision of potassium.

MAGNESIUM

Approximately half of total magnesium content is present in bone, and the remainder is predominantly intracellular. The adult, therefore,

has double the infant's magnesium content. If the analytical data are corrected for bone magnesium, the discrepancy is small and readily explained by the greater muscularity of the adult. With the information presently available, no distinction can be drawn between magnesium metabolism in infancy and at maturity. No instance of dietary magnesium deficiency in man has been recorded, in contrast to the numerous examples of striking clinical magnesium deficiency syndromes in domestic and laboratory animals. The magnesium requirement for growth is automatically provided by calorically adequate diets in man.

Walker and Vallee,[32] in a recent review of magnesium metabolism, emphasize the fact that technical problems have long impeded progress in this area of study. Though magnesium is essential as an activator of numerous enzymes and active pharmacologically in the regulation of nerve impulse transmission, the mechanisms governing its concentration in body fluids remain obscure. The presence of a large skeletal depot suggests that a blood-bone equilibrium may tend to stabilize plasma magnesium, but the factors involved in such an equilibrium are poorly understood. It is known that bone may supply magnesium to extracellular fluid in the presence of dietary deficiency in animals. Acidosis seems to have no effect on bone magnesium, in contrast to its influence upon sodium, calcium, carbonate and (probably) potassium.[1, 2]

CALCIUM

The measurement of calcium is relatively simple when large samples are available. The quantitative difference between infant and adult shown in Table 1 can easily be explained on the basis of a similar difference in mass and mineralization of the skeleton. Since calcium may serve as a source of urinary base in both acute and chronic acidosis, the adult is evidently more secure than the infant in that he has more calcium and a higher ratio of calcium carbonate to calcium phosphate. The quantity of skeletal calcium available in acute situations has not been indicated by appropriate rate studies. The amount which may be gradually withdrawn by chronic renal base loss is large.

Less than 1 per cent of total body calcium is in solution, and of this at least half is protein-bound. The remaining minute fraction present as ionized calcium is responsible for the physiologic effects of this element. The measurement of ionized calcium is exceedingly difficult, with the result that data on total calcium content of the body or of specific tissues or phases have only limited significance in terms of function. Plasma ionized calcium concentration is the resultant of a bewildering array of opposing forces. The blood-bone equilibrium is affected by Parathormone, pH, bone vascularity, age (as it influences the microstructure of bone) and the rate of resorption and deposition

of mineral at the time of study. The proportion of plasma calcium ionized is in turn determined by plasma protein concentration, pH, phosphate level and probably factors as yet unknown.

The newborn seems especially susceptible to derangements of ionized calcium (causing neonatal tetany) in the absence of obvious disease. Gardner and his co-workers[18] discussed this phenomenon in terms of parathyroid and renal immaturity in combination with phosphate loads, pointing out the relatively high phosphorus content of formula as compared to breast milk and the rarity of tetany in breast-fed babies.

Table 2 shows that calcium intake is always negligible in proportion to body content. However, the ratio of intake to growth requirement is in general lower than in the cases of sodium, potassium and water. Furthermore, two particularly low points are seen, one during the first year and one at age 12 to 14 (data for female subjects). These ages correspond to periods of rapid growth. From consideration of composition and growth rates, therefore, two inferences may be drawn, both of which have long been common clinical knowledge. The first is that calcium, in contrast to sodium and potassium, may be implicated in growth failure in spite of its relative abundance in the body. The second is that two periods, infancy and adolescence, are particularly hazardous in this respect. Close attention to calcium and vitamin D intake in early childhood is the rule; neither parents nor physicians are equally sensitive to the precarious state of calcium balance in adolescence. Johnston[22] presents the problem in detail, mentioning the definite threat of rickets and the possible correlation of slipped epiphysis with defective mineralization.

PHOSPHORUS

Phosphorus, like calcium, is present chiefly in bone. As might therefore be expected, Table 1 shows that infants contain relatively little of this element. Darrow found that correction of total body content by subtraction of bone mineral resulted in practically equal figures for newborn and adult (women).[10]

As an electrolyte, phosphorus makes up a small portion of plasma anions and serves as an important urinary buffer. Its vital functions in energy transfer are outside the scope of this paper. The status of cell water phosphorus is obscure, since no definite valence can be assigned. Skeletal phosphorus is said to be readily available to extracellular fluid,[27] and plasma phosphate must, therefore, reflect an equilibrium or, as Darrow more correctly phrases it, "a biological steady state."[9] Daily intake, again as in the case of calcium, comprises only a minute fraction of total content. Parathyroid activity regulates plasma phosphate concentration by altering the ratio of renal tubular resorp-

tion to filtration and also by directly influencing the availability of bone phosphate. By what means these ends are achieved is at present obscure. The importance of the parathyroid-renal axis in phosphorus regulation is indicated by several natural experiments: hypoparathyroidism, resulting in hyperphosphatemia, renal rickets or "phosphate diabetes," in which a tubular defect results in continual phosphate wastage with consequent rickets, and the converse states of hyperparathyroidism and chronic renal insufficiency, leading, respectively, to hypophosphatemia and hyperphosphatemia.

The growth requirement for phosphorus so closely parallels that for calcium that separate discussion would be redundant. The close association of these two elements in a single principal dietary source (milk and milk derivatives) makes it likely that attention to either will result in adequate provision of both.

CARBONATE

Carbonate is unique among the electrolytes in that it is a by-product of metabolism. There is no dietary requirement for this ubiquitous and useful cation, aptly styled a "mendicant" by Gamble since its concentration varies inversely with that of other proton acceptors, usually in a passive fashion. The buffer function of extracellular bicarbonate is universally appreciated. The differential between extracellular and intracellular bicarbonate is approximately 2/1, while carbonic acid is considered to be freely diffusible. The consequences of this are discussed by Wallace and Hastings,[33] with the conclusion that intracellular pH is probably 6.8.

Carbonate is predominantly skeletal in location, with the result that adult content is nearly double that of the infant. Skeletal carbonate is an active participant in total electrolyte metabolism.[4, 20, 27] In animals, skeletal carbonate can be altered by drastic long-term distortions of the dietary calcium-phosphate ratio. While bone buffering capacity can probably be changed in this manner, no clinical application is apparent.

SUMMARY

This presentation has two chief objectives. First, a distinction is drawn between survival and normal growth as criteria for assessing the importance of any specific mineral intake or assimilation. The relative importance of these factors will depend on the ratio of turnover to content as compared to the ratio of turnover to growth requirement. Intelligent evaluation requires knowledge of body composition at various ages as well as growth rate at the particular time under consideration. Much of our body composition data comprises a combination of animal studies with wide extrapolations from a few human analyses.

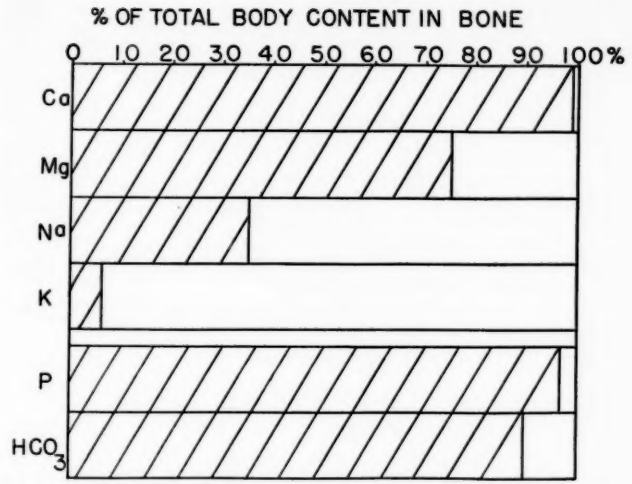

Fig. 1. Percentage of total body content in bone, calculated from data for adult human bone.

Secondly, the importance of blood-bone transfers in determining plasma concentration of several constituents has become evident. Figure 1 represents the relationship between bone and body composition. At present our understanding of bone chemistry, especially of rates of exchange and regulatory mechanisms, is not extensive enough to be of much use clinically. Neuman and Neuman[27] have recently published a thorough discussion of the subject. Advances in the management of renal disease, of certain orthopedic problems, and of exposure to radioisotopes may be expected as our knowledge of this particular aspect of body composition is extended.

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766 Irving Avenue
Syracuse 10, New York

ACIDOSIS AND ALKALOSIS

LEWIS A. BARNESS, M.D.

Acidosis and alkalosis are simple concepts involving a change in the pH of the serum; the effects of either acidosis or alkalosis are so devastating that the body has made many provisions to help prevent change in pH and maintain homeostasis. Unfortunately, pH may not be determined in some laboratories for varied reasons, and physicians sometimes forget the definitions of acidosis and alkalosis. The normal pH of the serum, that is, the pH of the serum at which the enzymatic processes of the body can proceed at rates considered normal, is pH 7.30 to 7.45. An increase in pH above 7.45 is alkalosis, and a decrease below 7.30 is acidosis.

When metabolic derangements cause acidosis, the serum carbon dioxide content* decreases below the normal of 22 to 26 mEq. per liter;

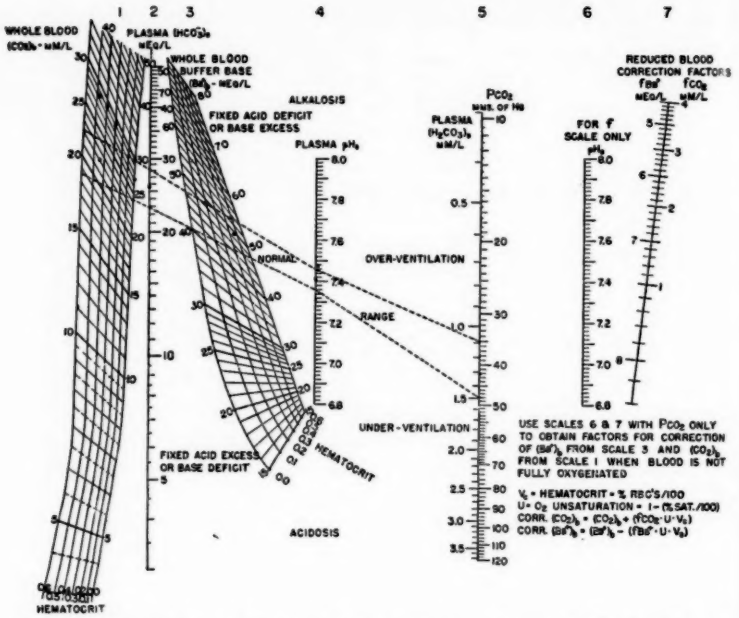
* Terminology relating to carbon dioxide in the serum is sometimes confusing. Carbon dioxide is carried in the blood in three forms: (1) bicarbonate, HCO_3^-, is the main form, with small amounts of (2) free carbon dioxide gas; and (3) carbon dioxide combined with water as carbonic acid, H_2CO_3.

Two methods for carbon dioxide determination are in common usage. *Total carbon dioxide* is the same as *carbon dioxide content*, and measures the most nearly physiologic status of the total of all three forms of carbon dioxide as it exists in the serum of the patient. Blood is drawn under oil, and the carbon dioxide in all forms is converted to carbon dioxide gas and measured. *Carbon dioxide-combining power* is numerically almost the same as carbon dioxide content. Blood is drawn without an oil seal and is equilibrated with the carbon dioxide of the technician's lungs and then is measured. It measures the ability of carbon dioxide to combine with the base present in the patient's serum, and is more a reflection of total base of the serum than of the carbon dioxide content.

Serum bicarbonate is not measured directly, but is calculated by a diagram such as that of Singer and Hastings (Fig. 2). Likewise, dissolved carbon dioxide or carbonic acid is not measured, but is calculated from a similar diagram. In clinical terminology, total carbon dioxide, carbon dioxide content, carbon dioxide-combining power and serum bicarbonate are used interchangeably. From a practical viewpoint, these differ little in the usual patient, though, physiologically, they differ in significance.

The *partial pressure of carbon dioxide*, pCO_2, is the same as *carbon dioxide tension*, and represents the carbon dioxide present as gas in the blood. This can be measured with a Haldane breathing apparatus by equilibrating lung carbon dioxide with serum gaseous carbon dioxide, though this is rarely performed in children.

From the Department of Pediatrics, University of Pennsylvania School of Medicine, and the Hospital of the University of Pennsylvania, Philadelphia.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WHOLE BLOOD
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WHOLE BLOOD BUFFER BASE
ALKALOSIS
FIXED ACID DEFICIT OR BASE EXCESS
PLASMA pH
NORMAL RANGE
OVER-VENTILATION
UNDER-VENTILATION
FIXED ACID EXCESS OR BASE DEFICIT
HEMATOCRIT
ACIDOSIS
REDUCED BLOOD CORRECTION FACTORS
FOR f SCALE ONLY
USE SCALES 6 & 7 WITH PCO2 ONLY TO OBTAIN FACTORS FOR CORRECTION OF (BB')b FROM SCALE 3 AND (CO2)b FROM SCALE 1 WHEN BLOOD IS NOT FULLY OXYGENATED
Vc = HEMATOCRIT = % RBC'S/100
U = O2 UNSATURATION = 1 - (% SAT./100)
CORR. (CO2)b = (CO2)b + (fCO2 · U · Vc)
CORR. (BB')b = (BB')b - (fBB' · U · Vc)

Fig. 2. Nomogram for the acid-base balance of human blood at 37° C. For oxygenated blood (scales 1 to 5) a straight line through given points on 2 of the scales intersects the remaining scales at simultaneously occurring values of the other variables. The position of the line indicates the kind and magnitude of any disturbance of the acid-base balance. The normal range is for arterial, not venous, blood. For details of use, see text. (From R. B. Singer and B. Hastings: *Medicine*, Vol. 27.)

and when metabolic derangements cause alkalosis, the serum bicarbonate rises. Because carbon dioxide content is easily determined in most laboratories, many clinicians make the natural error of assuming that *any* low serum carbon dioxide content represents acidosis, and any high carbon dioxide content, alkalosis. Not only is this an error in definition, but also, when carbon dioxide content is raised because of inability of the lungs to exchange carbon dioxide for oxygen, as may occur in severe pneumonia, a respiratory *acidosis* exists with an elevated serum carbon dioxide content, and treatment for alkalosis may be disastrous.

BODY MECHANISMS FOR MAINTENANCE OF pH

Buffers

Buffers may be composed of weak acids, such as acetic acid, and their salts (e.g., sodium acetate), or weak bases (e.g., ammonium hydroxide) and their salts (e.g., ammonium chloride). The property of the buffer

of importance in maintaining homeostasis is that it resists change in pH when approximately equal molar quantities of acid (or base) and its salt are present.

Four buffers are of great importance in resisting change of pH of the blood. Some of these are coarse adjusters; i.e., they resist large changes in blood pH and keep the serum within the limits of, say, pH 7.0 to 7.8; whereas other buffers are more delicate—the fine adjusters—and resist even small changes in pH.

1. Bicarbonate-Carbonic Acid System. That buffer which resists even smallest changes in pH—the finest of the body buffers—is the bicarbonate-carbonic acid system: a weak acid and its salt. The pH of bicarbonate, like the pH of any weak acid and its salt, is determined by the Henderson-Hasselbalch equation:

$$pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]}.^*$$

At pH 7.4 the ratio of salt to acid is approximately 20:1: i.e., in normal serum there are 20 mols of bicarbonate ion to each mol of undissociated carbonic acid.

The four possible variations in concentration of bicarbonate and carbonic acid are as follows: (1) Bicarbonate may rise in relation to carbonic acid, and pH will rise, typical of the alkalosis of metabolic diseases such as occurs with vomiting of pyloric stenosis. (2) Bicarbonate may fall in relation to carbonic acid, and pH will fall, as in metabolic acidosis of diarrhea. (3) Carbonic acid may rise in relation to bicarbonate, as in acidosis of poor respiratory exchange. (4) Carbonic acid may decrease out of proportion to a decrease in bicarbonate:respiratory alkalosis, as is seen with hyperventilation.

Actually, there are only some 25 mols of bicarbonate in a liter of serum—a very small total quantity and a very small absolute buffer capacity. The prime importance of bicarbonate in the regulation of pH

* $[H^+]$ is concentration of hydrogen ion in solution. At neutrality there are 10^{-7} mols of H^+ in solution. pH is the negative logarithm of the concentration of hydrogen ion; i.e., at neutrality, pH = 7. K is the dissociation constant of an acid or base, and is determined by the formula for the acid HA:

$$K = \frac{[H^+]\,[A^-]}{[HA]},$$

where $[H^+]$ is the hydrogen ion concentration, $[A^-]$ the anion concentration, and [HA] the concentration of the undissociated acid. pK, like pH, is the negative logarithm of this dissociation constant. As in the bicarbonate equation:

$$pH = pK + \log \frac{\text{salt}}{\text{acid}}$$

when the concentration of salt equals the concentration of acid, pH = pK (since $\log 1 = 0$). Or the pK of an acid equals the pH when the salt and undissociated acid are present in equal quantities. For carbonic acid, pK = 6.1.

lies rather in the ease of adjustment of proportion of salt and acid via the lungs. Carbonic acid, H_2CO_3, for example, is easily hydrolyzed to water and carbon dioxide. Carbon dioxide increases and is followed by a more rapid exchange of carbon dioxide out of the serum into the alveoli, and out into the air. If the partial pressure of carbon dioxide in the serum is lowered, there will be a slower exchange through the lungs.

A similar mechanism for removal or retention of carbon dioxide exists in the kidney, again contributing to the rapid adjustment of salt and acid to bring the pH to 7.4.

2. Serum Proteins. A cruder buffer system is that afforded by serum proteins. Each molecule of a protein contains many free basic (amino) groups and many free acidic (carboxyl) groups. If one acid molecule, e.g., hydrochloric acid, should be present in the serum, it would attach easily to a free amino group and form a neutral salt at that point of the molecule, thereby changing the pH of the solution very little. Likewise, a free base, e.g., sodium hydroxide, would form a neutral salt on a free carboxyl group of the protein. Since the proteins account for 7 per cent by weight of the serum, they represent a large potential buffering capacity.

3. Hemoglobin. Hemoglobin operates as a buffer in two different ways. First, small amounts of hemoglobin are present as free hemoglobin in the serum and contribute their buffering capacity similar to that of any protein. Secondly, and probably of more physiologic importance, oxygenated hemoglobin behaves as a weak acid to its salt, hemoglobin, and performs like the usual buffer system. Of course hemoglobin is an important intracellular buffer within the red blood cell.

4. Phosphoric Acid. Phosphoric acid, H_3PO_4, has three dissociation constants: pK_1, 1.96; pK_2, 6.7; pK_3, 12.4. In the serum, only the second dissociation constant, $HPO_3 = /H_2PO_3^-$, is important as a buffer.

Kidney

An agent equally important as buffers in the maintenance of the pH is the kidney. Several renal mechanisms for pH regulation have been delineated. Of these, at least three are important.

1. Carbonic Acid Excretion and Reabsorption have already been mentioned.

2. Conservation of Base by Ammonia Formation. The sum of cations such as sodium and potassium, calcium and magnesium equals the sum of anions (Fig. 3). Free cations such as sodium are hydrolyzed in the presence of water to the strong base sodium hydroxide. For apparently good semantic reasons, cations are therefore termed "bases."

If one chloride ion were to be excreted by the kidney of a child with acidosis, it could not proceed down the renal tubule as Cl^-, since nature

abhors a free ion. A cation such as sodium would be a requisite accompaniment of the anion. The kidney makes available for excretion ammonia, a weak base, which in the presence of an anion can become the cation, ammonium. The kidney thereby excretes one molecule of *ammonium* chloride, and the sodium ion remains (or is conserved) in

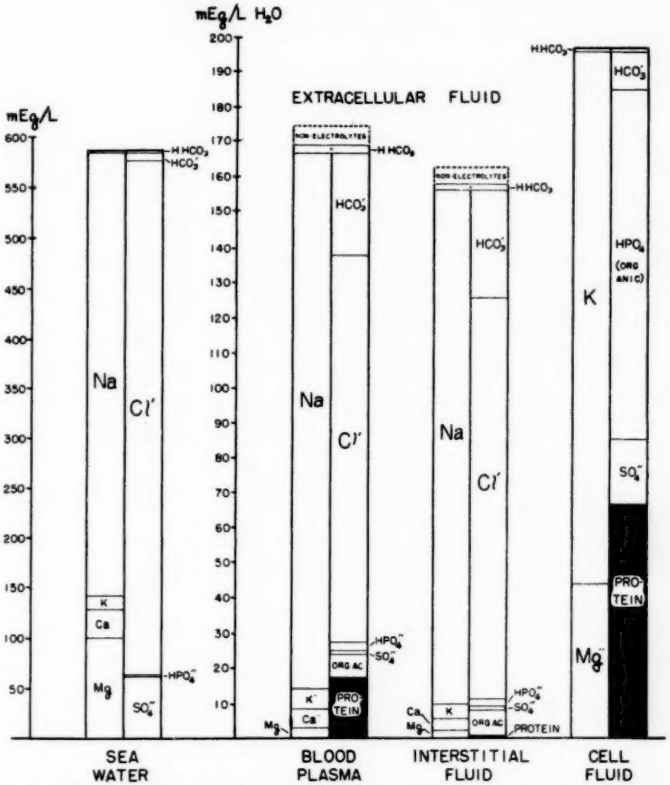

Fig. 3. Equality of the sum of the cations and of the anions in various fluids. (From J. L. Gamble: *Extracellular Fluids*. Cambridge, Harvard University Press.)

the serum to continue to act as a base. If the serum is alkalotic, regulatory mechanisms of ammonia production are such that no ammonia would be formed, and sodium would be excreted as *sodium* chloride or *sodium* bicarbonate.

3. Conservation of Base. *Phosphate Excretion.* At the usual urinary pH, phosphate exists either as $H_2PO_4^-$ or $HPO_4^=$. In the serum the more alkaline $HPO_4^=$ is prevalent. By adding one hydrogen ion to

$HPO_4^=$, the urine becomes more acid, and a molecule of base is retained or conserved.

Other mechanisms of renal conservation of base, such as the excretion of organic acids, are equally important when large quantities of organic acid are present in the serum. Thus diacetic acid, formed in the incomplete breakdown of carbohydrate in diabetic acidosis, may be excreted unchanged in the urine. Likewise, in alkalosis, an alkaline urine may be formed, owing to increased excretion of base.

FACTORS CAUSING ACIDOSIS AND ALKALOSIS

Acidosis and alkalosis are caused either by excess loss of alkali or acid, respectively, or by excess production or ingestion of acid or base. All mechanisms may operate simultaneously.

Most commonly in pediatric practice acidosis is seen in infants with *diarrhea*. Here the important bases, sodium and potassium, are lost first in the stool. As water is also lost, the homeostatic mechanisms listed above are first operative, and later, especially as the liver and kidney no longer work effectively, base spills into the urine in increased quantities. As the liver fails, fatty acids are not metabolized completely and likewise contribute to the metabolic acidosis. Failure of the liver to completely metabolize simple organic acids to carbon dioxide and water is the chief reason why acidosis occurs much more rapidly in premature and young infants with an innately immature liver than in the older child.

In such states as *pyloric stenosis*, hydrochloric acid is vomited from the stomach. Early in the disease a metabolic alkalosis is found, due to excess loss of chloride with no compensating loss of sodium. Again, however, as the infant continues to vomit, he becomes dehydrated, and organic acids accumulate from liver insufficiency. Late in the disease, therefore, a metabolic acidosis is superimposed on the metabolic alkalosis, and the pH of the serum may be normal or even lower than normal in the severely ill infant with pyloric stenosis.

In children with *respiratory obstructive disease*, especially diseases involving the alveoli, the diseased lungs are unable to excrete the normally produced carbon dioxide. Carbonic acid therefore accumulates without a proportional increase in serum bicarbonate, and respiratory acidosis occurs. As the child becomes acidotic, he eats less, and a state of starvation occurs. The child begins to consume his own tissues, but is unable to metabolize these tissues beyond the state of simple organic acids. Thus a metabolic acidosis adds to the already present respiratory acidosis.

In children with *hyperventilation*, which may occur for many reasons and is most frequently seen with encephalitis or aspirin intoxication, and

was formerly seen in respirators which were operating too rapidly, the carbon dioxide of the lung is too completely removed into the atmosphere. The carbonic acid of the serum decreases more rapidly than the bicarbonate, and respiratory alkalosis results. The kidney attempts to correct for the respiratory alkalosis by excreting base. If the child stops eating or becomes dehydrated, a metabolic acidosis will develop with the respiratory alkalosis. The pH of the serum will depend on which of the processes is more prominent. An excellent discussion of respiratory alkalosis followed by the metabolic acidosis of salicylate poisoning is presented later (p. 281*ff.*).

Metabolic alkalosis following intracellular potassium deficiency is described in the clinic on renal disease (p. 123*ff.*).

PATHOLOGIC CHANGES OCCURRING WITH ACIDOSIS AND ALKALOSIS

Although the primary disease is usually responsible for the pathologic state of the ill child, acidosis and alkalosis per se can cause further damage, thereby continuing the morbid state after the original disease has disappeared. The mechanism of these changes is not well delineated, but logical assumptions have been made.

Change in Cellular Integrity. The cell wall is prepared to withstand a pH of 7.4 with little variation. These walls are fragile semipermeable membranes, protecting the inner cytoplasm and nucleus from change. A small change in pH changes, for example, the intracellular content of potassium and sodium. The intracellular potassium decreases; the sodium increases. These ions have chemical and physicochemical functions in the cell. The physicochemical changes in particular may lead to complete breakdown of the cell with loss of structure and function.

Enzymatic Changes. Each enzyme operates at an optimal pH. Many enzymes operate better at a pH that differs from 7.4. Nevertheless bodily adjustments are such that, for the total human body, reactions proceed at the rate best suitable to the total organism when the serum pH is 7.4. At a different pH some vital reactions are speeded and some slowed, resulting in imbalance and further destruction.

Extracellular Changes. Certain bodily reactions are sensitive to the pH of the serum. Among these are the transmission of nerve impulses and the relative proportion of serum electrolytes. An increase in pH, for example, decreases the ionized calcium in the serum and may result in tetany (see p. 201*ff.*). A low serum potassium may decrease nerve transmission, especially in the heart or to the intestine. Many other examples are known.

Thus acidosis or alkalosis per se may affect all organs and all bodily functions.

COMPENSATED ACIDOSIS AND ALKALOSIS

As any disease begins to cause acidosis or alkalosis, the body calls on its reserves to prevent these states. So far as the body succeeds, compensation occurs. Compensation may be seen clinically, e.g., in the severe nephritic with a high retention of organic acids with almost negligible acidosis, or compensation can be better estimated by a study of the serum electrolytes. A simplified chart is as follows:

	pH	CO_2	Na	Cl	Organic Acids
Normal	7.30–7.45	22–26	136–145	95–100	Approx. 20
Respiratory acidosis,	↓ ↓	↑ ↑	→ or ↓	→	→
compensated	↓	↑	→ or ↑	→ or ↓	→ or ↓
Respiratory alkalosis,	↑ ↑	↓ ↓	→ or ↑	→	→
compensated	↑	↓	→ or ↓	→ or ↑	→ or ↑
Metabolic acidosis,*	↓ ↓	↓ ↓	↓	↑	↑
compensated	↓	↓	↓ or →	→ or ↓	↑ or →
Metabolic alkalosis,	↑ ↑	↑ ↑	→ or ↑	↓ ↓	↑
compensated	↑	↑	→ or ↓	↓	↑ or →

* Dehydration may occur out of proportion to salt loss. Thus Na and Cl in the serum will both be elevated. This is hyperelectrolytemia with metabolic acidosis, and is discussed in detail in the clinic on hyperelectrolytemia (p. 193*ff*.).

SYMPTOMS AND SIGNS OF ACIDOSIS AND ALKALOSIS

The disease states discussed in the second section of this symposium have their individual distinct signs and symptoms. A few general signs and symptoms sometimes help to distinguish acidosis from alkalosis.

The child with *metabolic acidosis* may have a history of diarrhea or starvation. He will usually have the sunken eyes and fontanels, dry tongue and parched skin of dehydration. In addition, he may be lethargic, or cyanotic with red lips, and have short, shallow or deep rapid respirations.

The child with *metabolic alkalosis* will ordinarily not be so dehydrated, and may be hyperirritable rather than lethargic. The lips will be deep cherry-red, and the respirations will be shallow—even sighing—and slow as he tries to retain carbon dioxide.

The child with *respiratory acidosis* will usually show signs of pulmonary disease in addition to the signs of metabolic acidosis; and the child with *respiratory alkalosis* will frequently have a history of ingestion of poison—or the signs and symptoms of encephalitis—in addition to the other signs of metabolic alkalosis.

TREATMENT OF ACIDOSIS AND ALKALOSIS

The entire second section of this symposium is concerned with the treatment of these states. Suffice it to say here that treatment is directed toward the steady repair of deficits with complete dependence of the physician on the patient to make the final necessary adjustments toward normality. Water alone or with a few minimal electrolytes with a good liver and good kidneys will most often correct even the most severe acidosis or alkalosis. The necessity for hypotonic solutions and potassium in the repair fluids is detailed in the clinic on diarrhea (p. 99*ff*.). Alkalinizing agents such as sixth-molar sodium bicarbonate are also discussed there, as well as acidifying agents. For respiratory acidosis, we are still limited almost entirely to administration of oxygen. For respiratory alkalosis, treatment consists mainly in the admonition not to treat for metabolic acidosis, and to treat rather the primary disease—again well discussed in the clinics on salicylism (p. 281*ff*.) and neurologic disorders (p. 257*ff*.).

SUMMARY

Acidosis and alkalosis are simple biochemical terms with complicated clinical significance. Acidosis and alkalosis can be determined only by measuring serum pH—a determination unfortunately not often done in clinical laboratories. Measuring serum carbon dioxide content, or the sum of carbon dioxide and chloride and subtracting from serum sodium, is a good approximation if one is sure he is dealing with metabolic acidosis or alkalosis. In the presence of respiratory disease these determinations are misleading and may result in completely incorrect treatment.

The normal infant has many able mechanisms to prevent or correct acidosis and alkalosis. A little judicious help is sometimes all that is required.

3600 Spruce Street
Philadelphia 4, Pennsylvania

THE PHYSIOLOGIC BASIS FOR ESTIMATING REQUIREMENTS FOR PARENTERAL FLUIDS

DANIEL C. DARROW, M.D.

A suitable system of fluid therapy should be based on three needs for water and electrolytes: (1) replacement of normal expenditure, (2) restoration of deficits, and (3) replacement of abnormal losses. The first two are discussed in this paper, while the third is considered in other parts of this symposium. Normal expenditure is related to total metabolism, deficit to body weight, and abnormal losses to the particular disturbances accompanying diseases. Consequently fluid requirements cannot safely be based on metabolic rate or body weight alone. It is true that the fluids administered must be given in such quantities and at such concentrations as to permit renal regulation of the volume and concentrations of body water. Considerable latitude in the composition and volume of parenteral fluids is permissible when renal function is normal. However, renal regulation is seriously limited when the kidneys are diseased, when disturbances in body composition have developed or when abnormal losses persist. Consequently physicians must understand the physiologic basis of normal expenditure, the probable magnitude of deficits and the characteristics of abnormal losses.

The normal expenditure of water is variable, owing to the physiologic regulation of dissipation of heat by the skin and the renal regulation of the volume of body water and the concentrations of serum electrolytes. Table 3 gives the amount of water lost by normal subjects under the usual circumstances.[6] The table also indicates that water expenditure may be estimated on the assumption that 1 square meter of surface area usually indicates the expenditure of 1000 calories per day during paren-

From the Department of Pediatrics, University of Kansas, and the Children's Mercy Hospital, Kansas City.

teral fluid therapy.[3, 14, 19] Certain difficulties with this assumption are mentioned later. The insensible loss is about 43 gm. per 100 calories in the absence of sweat. About one third is contained in expired air, and the rest leaves the body by diffusion through the skin when there is no sweat. Usually about 20 gm. of sweat are formed.[12] The stools contain a small and relatively constant amount of water when there is no diarrhea, and during fluid therapy the amount may be practically nought. Urine volume can vary considerably in response to the requirements for regulation of body water and electrolytes. It is the possibility of varying urine water that permits variation in the water intake.

Based on the data of Du Bois,[9] Figure 4 represents diagrammatically the physiologic responses of the skin in the regulation of heat losses when environmental temperature varies. Between 80 and 84° F. (26.6

TABLE 3. *Usual Expenditure of Water in Ml. per 100 Calories Metabolized*

Insensible:	
Lungs	14
Skin	28
Sweat	20
Stool	8
Urine	80
Total	150

The loss of sodium, chloride and potassium is about 2–3 mEq. each.
The requirement per square meter of surface area is about 10 times these figures.

and 28.8° C.) the quiet nude subject is able to maintain body and skin temperature without sweating. The regulation is attained largely by alterations in skin circulation. Below this environmental temperature skin and body temperatures tend to fall. When body temperature decreases about 1.5° C., heat production increases, owing to a chill. Above the zone of comfortable adjustment, loss of heat by evaporation of sweat maintains skin and body temperatures. As environmental temperature approaches body temperature, all heat loss is accomplished by evaporation of water. Except at high humidity and temperatures, the rate of evaporation of water is not so diminished as seriously to interfere with heat dissipation except when metabolism is increased. In the absence of sweat, diffusion of water through the skin is dependent on the difference between vapor tension of the skin and that of the surrounding air. The vapor tension of the skin varies directly with skin temperature, while that of the air depends on environmental temperature and humidity. The air entering the lungs becomes 95 per cent saturated at close to body temperature. Cold air always contains relatively little moisture, while hot air is likely to have a low humidity. Consequently

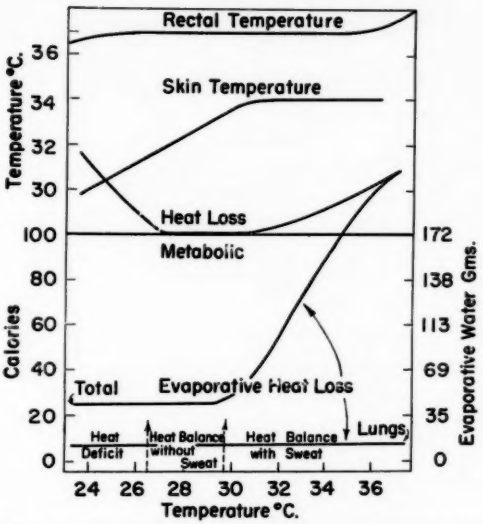

Fig. 4. Diagram of heat balance at different temperatures in nude adults.

loss of water through the lungs is usually approximately proportional to the volume of ventilation, which in turn is proportional to total metabolism. However, in hyperpnea the loss of water from the lungs may increase fivefold from the usual relation to metabolism. It should be noted that sweat is about 100 gm. per 100 calories at 95° F. (36.5° C.).

PRINCIPLES OF PARENTERAL FLUID REQUIREMENTS

The kidneys may excrete the required substances in a small volume of concentrated urine with high specific gravity or a large volume with low specific gravity.[6, 19] In terms of renal physiology concentrations are best expressed as osmols, the maximal dilution being a little less than 100 milliosmols per liter, and the maximal concentration 1400 milliosmols per liter. Since the osmolar concentration of serum is about 300 milliosmols per liter of water, urine concentration near this level involves minimal osmotic work. If water intake is able to permit renal excretion of the required substances at concentrations between 200 and 400 milliosmols per liter, the normal kidneys can excrete more water in a dilute urine or conserve body water by excreting a concentrated urine. When renal function is limited by renal disease or certain extrarenal disturbances, urine concentration may be limited to values close to that of serum. In the absence of antidiuretic hormone only dilute urine is formed, while in the presence of antidiuretic hormone the normal kid-

neys excrete concentrated urine. When oliguria or anuria develops, owing to intrinsic renal disease, urinary losses of water and electrolytes by the kidneys are absent and should not be included in fluids calculated to meet maintenance expenditure. In clinical practice the specific gravity of the urine suffices to indicate osmolar concentration. A very dilute urine may indicate that too much water is being administered, while a concentrated urine indicates that more water is desirable. Fluid therapy is planned with these facts in mind.

For example, the appropriate volume may be calculated from the relationship

$$mOsm = VC$$

in which *mOsm* is the excretory load in milliosmols, V is the volume in liters, and C the concentration in milliosmols per liter. The usual diet requires the excretion of about 40 milliosmols per 100 calories. During fluid therapy with appropriate amounts of salts the excretory load is about 25 milliosmols per 100 calories. The load is as low as 12 milliosmols on human milk. It should be noticed that the equation indicates that there is a maximal and minimal rate of excretion of water for a given excretion of osmols. For example, the osmolar load of the usual diet permits the excretion of 400 ml. of water at 100 milliosmols per liter and 25 ml. at 1400 milliosmols per liter per 100 calories. During parenteral fluid therapy the corresponding figures would be 250 and 18 ml. per 100 calories. Patients are unlikely to achieve maximal or minimal concentrations. Consequently it is important to provide fluids permitting excretion of urine containing the excretory load at concentrations which do not require considerable dilution or concentration.

To achieve this end, fluid should be prescribed to cover normal expenditure as indicated in Table 3, namely, about 150 ml. per 100 calories metabolized. To this amount of water the expected loss of sodium, chloride and potassium should be added. While normal kidneys can excrete urine practically devoid of sodium and chloride, some sodium and chloride are usually excreted. Normal stools contain negligible amounts of sodium and chloride, but appreciable potassium. The kidneys usually excrete 25 to 40 mEq. of potassium per liter even when potassium deficiency is developing. Nevertheless the kidneys can excrete as little as 4 mEq. per liter. Small amounts of sodium, chloride and potassium are lost from the skin even when little sweat is formed. Usually sweat contains 25 to 50 mEq. of sodium and chloride and about 15 mEq. of potassium per liter. Allowing for all these more or less obligatory losses, the requirements for sodium, chloride and potassium are about 2 to 3 mEq. of each per 100 calories metabolized. This estimate is a little more than the minimal, but the excess is seldom more than can be readily excreted. An appropriate mixture can be made by

adding one sixth or one fifth of the volume to 5 or 10 per cent glucose in water, using either physiologic saline or Hartmann's lactate Ringer solution. To this mixture add 20 millimols of potassium chloride per liter. The final concentrations should be about 20 mEq. each of sodium and potassium and 40 mEq. of chloride per liter, or the same concentrations of sodium and potassium and 20 mEq. of chloride and 20 of bicarbonate or lactate. One hundred and fifty milliliters of these solutions per 100 calories metabolized meet normal expenditure and provide a small excess which permits renal adjustment when body composition is close to normal and abnormal losses are small.

Total metabolism cannot be precisely estimated in a clinical situation. It is somewhat greater than basal metabolism during parenteral fluid therapy, but less than caloric intake under normal circumstances. Fever raises total metabolism about 12 per cent per degree C. of fever

TABLE 4. *Calories Expended per 24 Hours during Fasting*

SUBJECT	CALORIES PER KG.
Newborn	45–50
3–10 kg.	60–80
10–15 kg.	45–65
15–25 kg.	40–50
25–35 kg.	35–40
35–60 kg.	30–35
Over 60 kg.	25–30

(7 per cent per degree F.). Activity and other factors alter metabolism. Table 4 shows the probable metabolism per kilogram per day during parenteral fluid therapy.

It is usually stated that basal metabolism correlates best with surface area. Nevertheless basal metabolism is lower per square meter in the newborn period and rises in infants weighing 6 to 10 kg. to levels higher than that characteristic of adults. Actually Talbot[18] found that metabolism correlated best with weight during the first year. Holliday and Segar[13] pointed out the high metabolic rates per kilogram or surface area in infants weighing 6 to 10 kg. However, they recommend 100 ml. of water per 100 calories metabolized, but they fail to take into account the reduction of metabolism during the fasting accompanying parenteral fluid therapy. By using their data and calculating total metabolism at levels more nearly correct, fluid requirement is about 140 ml. per 100 calories, or 150 if water of oxidation is included.

Oliver, Graham and Wilson[17] reject the whole concept of computing fluid requirements from surface area. In addition to the awkwardness of computing surface area from weight, the implied relationship between surface area and metabolism is considered unwarranted. First, sufficient

measurements are not available for infants and children to justify confidence in the estimates of surface area. Second, if surface area is computed in the usual way, Talbot found that basal metabolism is higher per square meter in subjects weighing 6 to 20 kg. than the accepted figure for adults. Third, physiologists have shown that Rubner's generalization is not verified in any precise way. Pediatricians will find tables giving metabolism per kilogram at different weights not only more convenient, but also more accurate. Nevertheless calculating fluid requirements on the assumption that 1000 calories are metabolized per square meter at all ages yields values that are suitable. The exception is in the newborn period; especially before food has been ingested, the rates should be reduced by one third.

I have recommended the calculation of normal maintenance fluid from total caloric expenditure largely in order to call attention to factors altering metabolism from the values expected for a patient of a given size. I have always felt that any rigid method of estimating total metabolism was likely to have an error as great as 25 per cent. I agree with some such rule of thumb as was recommended by Oliver and associates.[17] The average values seem a little high for the metabolic rates during the fasting accompanying parenteral fluid therapy. They recommend the following fluids for maintenance: under one year, 150 ± 30; one to five years, 120 ± 30; children over five, 90 ± 30. I would call attention to the likelihood that some of the variations depend on alterations in metabolic rate that can be roughly estimated. Also I would expect the deviations from the average to become smaller as fluid requirement decreases per kilogram of body weight.

SODIUM

Although one cannot estimate precisely the deficits of water and electrolytes in a clinical situation, the probable maximal deficits can be calculated for water and sodium. The calculations involve a number of approximations and the assumption that the changes in serum sodium concentration result from a change in extracellular sodium without alteration of body water, or a change in body water without alteration in body sodium. The reader is referred elsewhere[5] for a discussion of body composition and the factors determining serum sodium concentration. The following method of calculation is seldom justified in patients because dehydration almost always involves both water and sodium. The calculation merely indicates how the order of magnitude of deficits may be estimated for simplified conditions and provides a physiologic basis for the probable maximal deficits of water and sodium in patients. The figure for water is essentially the one found in observations on man under heat stress,[1] and the one for sodium is essentially the one found

for dogs deprived of extracellular electrolyte without change in body water.[7]

Assuming osmotic equilibrium between extracellular and intracellular fluids,

$$\left(\frac{\text{osm}_r + \text{osm}_d}{W}\right)_e = \left(\frac{\text{osm}_r + \text{osm}_d}{W}\right)_i$$

where *osm* is osmotically active substances in body water and subscripts *r* and *d* refer respectively to osmols restricted to one compartment and those freely diffusible in body water. Subscripts *e* and *i* indicate extracellular and intracellular compartments. *W* is water in liters. Because osmols that are freely diffusible exist at the same concentration in all body water, osm_d may be omitted from the equation describing the factors determining serum sodium concentration and distribution of body water. Because the anions neutralizing sodium are predominantly univalent in extracellular fluids, the restricted osmols of extracellular fluid are approximately 2 Na_e and the restricted osmolar concentration is approximately twice the concentration of sodium in serum water, which is represented as $2[Na]_e$

Hence

$$2[Na]_e = \left(\frac{\text{osm}_r}{W}\right)_i = \frac{(2Na_e + \text{osm}_r)}{W_e + W_i}$$

Using simultaneous equations with a serum sodium value of 140 for normal concentration,

$$\triangle (Na)_e = ([Na]_e - 140)\, W_t$$

where W_t is total body water. The equation indicates that the deficit of sodium producing a serum sodium concentration of 110 mEq. per liter is 18 mEq. per kilogram when body water is 0.6 and remains constant. This estimate is probably too large, because intracellular osmols decrease when serum sodium concentration diminishes.[15] It is likely that the deficit is about 15 mEq. per kilogram—the amount of sodium in 100 ml. of physiologic saline.

Developing a similar equation when extracellular sodium is constant and water varies,

$$\triangle W = \left(1 - \frac{140}{[Na]_e}\right) W_t$$

For a rise in serum sodium to 170 mEq. per liter, owing to change in body water alone, about 120 ml. of water per kilogram would have to be removed from the body. Owing to increase in intracellular osmols, this is probably an overestimate.[15] It is likely that loss of 100 ml. per kilogram would produce this rise in serum sodium concentration.

Balance studies[4, 8] indicate that about one third of extracellular sodium and water is lost in isotonic dehydration of severe degree. This

is equivalent to about 80 ml. per kilogram of saline in infants and 60 in children and adults.

Accordingly, the physiologic evidence indicates that deficits of water seldom are greater than 100 ml. per kilogram; the deficits of sodium are likely to be less than the amount contained in this volume of saline, i.e., 6 to 8 mEq. per kilogram. One is justified as a rule of thumb in assuming that severe dehydration involves loss of about 100 ml. of water that should be replaced; the deficit of sodium that should be replaced is usually contained in about 0.6 of this volume of saline. In hypotonic states the deficit of sodium is greater, and the deficit of water is much less. The deficiency of sodium may be as great as 15 mEq., particularly when there is practically no true deficit of water. In hypertonic dehydration the deficit of sodium may be negligible. If excessive sodium has been given, there may be an excess of sodium in hypertonic states, and the deficit of water is in part a deficit relative to the excess of sodium. Moderate dehydration should be considered to involve smaller deficits. It is true that rapid losses of weight indicate that replaceable deficits of water are frequently greater than 100 ml. per kilogram. To some extent losses of weight involve losses of cytoplasmic structures due to starvation and tissue injury. These losses of water are replaced more slowly and only when food can be given. The foregoing estimates merely indicate the magnitude of the replacements that should be given rapidly, within one or possibly two days. Occasionally the deficits of water which should be rapidly replaced are greater than 100 ml. per kilogram.

Fortunately successful therapy does not depend on precise, rapid correction of disturbances in concentration, though the evidence indicates that the volume of extracellular fluid, particularly decreases in blood volume, should be rapidly replaced. For example, the shock accompanying severe isotonic dehydration due to loss of extracellular water and electrolytes should be rapidly corrected by restoring the volume of extracellular fluids with 60 to 80 ml. per kilogram of saline or Hartmann's lactate Ringer solution. Also the disturbances accompanying a notable decrease in serum sodium concentration due to loss of sodium are greatly benefited by rapidly increasing serum sodium concentration by injecting 15 mEq. per kilogram of sodium in a solution 2 to 3 times as concentrated as physiologic saline. It is advisable to give only half this amount immediately and, if the effect is favorable, repeat the injection after a few hours. However, it is not advisable rapidly to reduce serum sodium concentration in hypertonic states by injecting large amounts of glucose in water. Convulsions have accompanied this type of treatment while serum sodium concentration was still high. The reaction seems to be analogous to the water intoxication observed when serum sodium is rapidly reduced below normal, owing to excessive retentions of water relative to sodium. In hypertonic states it suffices to

give fluids that contain enough sodium to replace the probable deficits of sodium during the first 24 hours and sufficient water to replace water deficits in the same period. In this way the kidneys adjust serum concentrations gradually. The important consideration in administering solutions containing sodium salts is not to change rapidly the electrolyte pattern, but to restore deficits with a mixture permitting renal regulation of volume and concentrations except for special indications mentioned above.

POTASSIUM

Tissue analyses of experimental animals and balances in patients indicate that the maximal deficit of potassium may be as great as 15 to 20 mEq. per kilogram of body weight. Serum potassium concentration varies inversely with pH. This relationship is at a lower level when cell potassium is deficient. Consequently, serum potassium tends to be low in metabolic alkalosis and high in metabolic acidosis. Deficiency of intracellular potassium occurs regularly in metabolic alkalosis[2] and is frequent in metabolic acidosis. When the serum sodium concentration is low, serum potassium is likely to be high. Under these circumstances administration of potassium is likely to result in greater and more prolonged elevation of serum potassium than when serum sodium is normal. Nevertheless serum potassium and serum sodium concentrations are an unreliable indication of deficiency of intracellular potassium. The diagnosis of potassium deficiency is made chiefly by knowing the conditions likely to be associated with this change in body composition. The large deficits occur in diarrhea, metabolic alkalosis, most types of acidosis, accompanying the use of corticosteroids, especially desoxycorticosterone, and following prolonged parenteral fluid therapy without potassium. The magnitude of the possible deficits indicates that three to five days are required for replacement. Potassium is included in practically all fluid therapy not only to replace deficits, but also to prevent deficits from developing.

Little difficulty has been encountered with potassium intoxication if a few simple rules are followed. The first precaution is to restore circulatory and renal functions by replacing deficits of water and extracellular electrolytes partially or completely before starting solutions containing potassium. Usually the injection of 20 to 40 ml. per kilogram of a mixture of equal parts of Hartmann's lactate Ringer and 5 or 10 per cent glucose in water over a period of 1 hour suffices. The remaining fluid for the first 24 hours may then be given with added potassium. Infants with potassium deficiency may receive 3 mEq. per kilogram in addition to the amount suggested for maintenance. Because children and adults have a lower urine volume per kilogram of body weight, one

usually limits the amount of potassium to 3 mEq. per kilogram. The rule is to limit the concentrations of potassium to less than 40 mEq. per liter in solutions injected intravenously. The potassium for one day should be given over as long a period as feasible and not in less than six hours. The use of potassium is almost invariably contraindicated in renal insufficiency and untreated adrenal insufficiency.

PHOSPHATE

One to 2 millimols of phosphate has been recommended for maintenance fluids per 100 calories metabolized. Cases of diabetic acidosis regularly develop low serum phosphate during recovery and retain rather large amounts when phosphate is given.[11] It is not clear that phosphate reduces mortality. The author did not find clear evidence of loss of phosphate from the cells in patients recovering from infantile diarrhea.[4, 8] However, studies of severe undernutrition in Mexico City show that the muscles develop striking deficiency in phosphorus along with increases in cell water and sodium.[16] Future studies should define the indications for phosphate therapy.

MAGNESIUM

Although the cells apparently do not readily lose magnesium in response to diets low in magnesium, some evidence of favorable response from magnesium has been found in alcoholics. At present clear evidence of magnesium deficiency in pediatrics is not at hand.

CALCIUM

The indications for calcium therapy would require more space than is warranted in this discussion. It should be mentioned that the development of low serum calcium following treatment of infantile diarrhea (the postacidotic state) is rare in my experience. Administration of excessive amounts of sodium bicarbonate and failure to include potassium apparently increase the likelihood of this complication.[10]

DEHYDRATION DUE TO DIARRHEA

With the foregoing background giving the magnitude of the deficits and normal expenditure, it is possible to calculate the fluid requirements for severe dehydration due to diarrhea. In this way one can compare the amounts of fluid indicated with weight and surface area. Table 5 shows the quantities of water, sodium, chloride and potassium required to replace the deficit, cover normal expenditure and replace continuing

abnormal losses. The examples chosen are a 3-kg. infant, a 30-kg. child and a 70-kg. adult. The deficit is 100 ml. of water per kilogram in the infant, but only 80 ml. in the others. The rate of stool losses was considered to be the same per unit of calorie production in all examples. The table shows the concentrations of electrolyte in the indicated fluids to be sufficiently alike to suggest that the differences are of little significance. However, the volumes in the three examples are significantly different if calculated by weight or surface area. It is appropriate to

TABLE 5. *Estimated Fluid Requirements in Severe Diarrhea with Dehydration (First Day)*

	NORMAL LOSS	DEFICIT REPLACEMENT	ABNORMAL LOSS	TOTAL	FLUID CONCENTRATION INDICATED		
					Per Liter	Per Kg.	Per M.²
3-Kg. Infant with Surface Area of 0.2 M.²							
Water (ml.)	360	300	75	735		245	3700
Na (mEq.)	7	27	4	38	52	13	190
Cl (mEq.)	7	27	4	38	52	13	190
K (mEq.)	7	9±	4	15*	20*	5*	75*
30-Kg. Child with Surface Area of 1 M.²							
Water (ml.)	1500	2400	375	4275		143	4375
Na (mEq.)	30	216	20	266	62	9	266
Cl (mEq.)	30	216	20	90	62	9	266
K (mEq.)	30	90±	20	90*	21*	3*	90*
70-Kg. Adult with Surface Area of 1.72 M.²							
Water (ml.)	2600	5600	645	8845		126	5150
Na (mEq.)	52	500	34	586	66	8	330
Cl (mEq.)	52	500	34	586	66	8	330
K (mEq.)	52	210±	34	210*	24*	3*	122*

* Deficit of potassium is probably greater than 3 mEq. per kilogram and cannot be replaced in 1 day. The amount accompanied by an asterisk is the safe dose for 1 day.

calculate normal expenditure on some function of total metabolism, but deficits should be estimated from weight.

Because renal function is approximately proportional to metabolic rate, it has been argued that renal function is able to adjust body water when appropriate fluids are given in proportion to surface area or some function of total metabolism. If the deficits are not great and if the disturbances in body composition are small, this is probably the case. Nevertheless systems of therapy prescribing fluid per unit of surface area have advocated solutions with different concentrations at different ages. In other words, fluids administered according to surface area do not elimi-

nate the necessity of providing water and electrolytes in varying amounts per unit of surface area. In the interest of clarity of thinking it is better not to try to bypass the relation of fluid requirements to two different dimensions, namely, expenditure to some function of total metabolism, and changes in body composition to body weight.

SUMMARY

Fluid therapy should be based on the estimation of deficits per unit of weight, normal expenditure on total metabolism, and abnormal losses on the nature of the disturbance. Although expenditure may be related to surface area, tables relating weight to calorie production give a more accurate estimate of total metabolism than one constant metabolic rate per square meter of surface area. Renal regulation of body water and electrolytes is the best friend of the doctor planning fluid therapy, but it cannot be depended on to adjust the volume and concentration of body water if the fluids prescribed for patients of different sizes are computed solely in relation to surface area and ignore the fact that deficits are best related to body weight.

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5847 Howe Drive
Mission, Kansas

SOME ASPECTS OF RENAL STRUCTURE AND FUNCTION CONCERNED WITH REGULATION OF THE BODY FLUIDS

JACK METCOFF, M.D.

The exact mechanism by which the kidneys regulate the composition of the body fluids is not known. Although intracellular fluids seem but remotely related to urine, regulation of the volume and composition of the extracellular body fluids defines the urinary function of the kidney. Since the major fluid compartments maintain a dynamic equilibrium, precise adjustment of their composition clearly depends upon the rate of filtration and the effectiveness of the kidney tubular reabsorptive mechanisms for extracting water and removing or rejecting solutes (chiefly sodium and accompanying anions) from the fluids flowing in the tubular lumen. Since water and solutes can be lost through other routes such as the gastrointestinal tract, skin and lungs, the kidney cannot be considered the only mechanism for regulation of the quantity and composition of the body fluids; nevertheless it sustains the chemical structure of extracellular fluid, and may be considered the organ *par excellence*[49a] of evolution, as indicated by Gamble[23] in his classic Syllabus. Because of their direct effects on tonicity and volume of body fluids, renal activities constitute the first line of defense of the body composition. At a normal filtration rate of 70 ml. per minute per square meter about 100 liters of glomerular filtrate are formed daily. This quantity would be equivalent to "turning over" the extracellular fluids some 15 times each 24 hours. Since about 1 liter of urine is formed during this period, the renal tubules must selectively readjust the composition of the 99 liters of filtrate reabsorbed; hence they modify the composition of the total extracellular fluid once each 90 to 100 minutes. The alterations in tonicity and ion concentration of the extracellular fluids result in secondary changes in the intracellular environment (and

possibly vice versa). Such predominantly cellular activities represent a second line of defense of body composition. Various humoral mechanisms further modify renal or tissue cell functions, and provide for integration of bodily adjustments.

The total body water comprises 60 to 80 per cent of body weight. The osmotic pressure (tonicity) of the body fluids is determined largely by the concentration of the solutes confined to the extracellular fluids. Increasing concentrations activate thirst and water reabsorption responses from the hypothalamus and neurohypophysis, respectively. The consequent water retention dilutes body fluids and restores isotonicity. Opposite effects attend decreased osmolarity of the extracellular fluids. However, isotonic expansion of the body fluids and the relative constancy of their volume are determined largely by the body content of sodium and chloride and potassium and phosphorus, the principal ions of the extracellular and intracellular fluids. Under normal conditions the extrarenal losses of sodium and potassium are small, and the quantities of these ions retained in the body are regulated by their excretion in the urine. With certain abnormal circumstances (severe dehydration, excessive water retention or salt depletion) regulation of volume may take precedence over regulation of tonicity. Therefore the volume and tonicity of the body fluids, although modified by several factors, are finally determined by the excretion of water and salt through the kidney.

This paper will endeavor to highlight some recent observations on, and hypotheses of, renal functions which clarify certain clinical problems.

NEW CONCEPTS OF RENAL STRUCTURE

The Glomerulus

The current embryologic concept that glomeruli develop into double-walled cups as a result of invagination of the proximal ends of developing renal tubules being pushed in by blood vessels appears to be erroneous. As pointed out by Hall,[33] over 100 years ago Gerlach[28] used the example of a man pulling on his "stocking nightcap" to illustrate his opinion of how the invagination "covers the glomerular capillaries with a continuous simple epithelial layer, such that the malpighian *rete mirabile* lies in an invaginated cell layer similar to the intestine in the peritoneum." The "stocking nightcap" has become outmoded by modern facilities; in similar fashion the concept of tubular invagination by a growing glomerular bud has been outmoded by new techniques of microdissection and electron microscopy.

Hall[33] presented preliminary evidence, derived from careful electron microscopic inspection of many sections from fetal rat kidneys, that the glomerulus differentiates *in situ* by proliferation and readjustments within the cells of the earliest anlage. The latter often appears as a compact mass of cells with no vesicular space. Capsular development appears to be initiated by a flattening of the cells of the parietal layer of Bowman's capsule. As the renal corpuscle develops, the parietal layer of Bowman's capsule presumably grows more rapidly than the cellular mass formed by the visceral layer of the capsule. Cells which are differentiating into capillaries seem to expand,

thus accounting for a slitlike separation of the layers in the irregular hollow sphere being formed. Cells of the visceral layer of Bowman's capsule differentiate into podocytes, having trabeculae which terminate in foot processes, the pedicels, long before the lumen of the capillaries becomes continuous or circulation is established. Hall has the impression that the larger processes of the podocytes penetrate between the undifferentiated cells and thereby possibly play a role in separating off sections of capillary endothelium which subsequently organize into characteristic capillary patterns.

From studies of latex-injected and microdissected glomeruli it became evident that the afferent arterioles of the glomeruli branch into a few major vessels, which in turn bifurcate into second-order branches which ultimately give off lateral capillaries. The

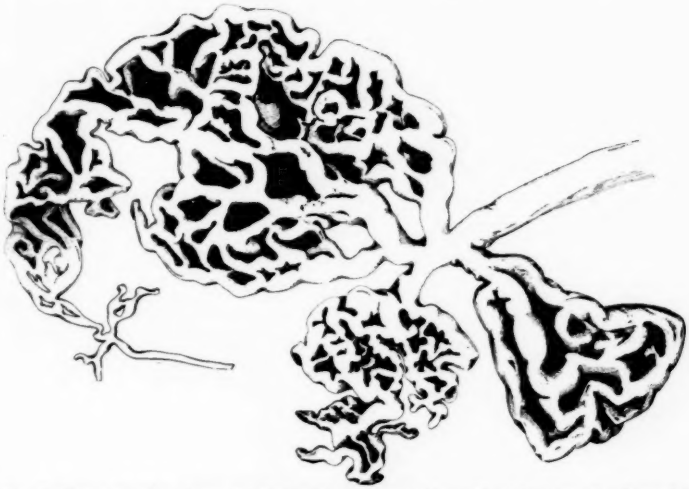


Fig. 5. Drawing of a dissected, latex-injected rat glomerulus showing the branching of the afferent arteriole into 3 basal vessels, each supplying one lobule. The lobule at the lower left is relatively intact, the middle one is partially flattened, and the efferent arteriole appears to extend from it. Note the anastomoses of the several branches arising from the main communicating lobular vessels. (The author is indebted to B. V. Hall for permission to reproduce this previously unpublished drawing.)

lateral capillaries anastomose with each other and the second-order vessels, forming a ladder-like structure.

Apparently each basal branch supplies one lobule. In general, the original bifurcation and later anastomosing capillaries of any single primary branch seem to make up the anatomic unit of the lobule. The observations utilizing new techniques extend, but are consistent with, the original surmise made by Carl Ludwig 100 years ago.[49] The seven or eight basal branches arising from the afferent arteriole, and subsequently yielding the lobular capillary network, taper and terminate in a short vessel which joins with similar vessels from other lobules of a glomerulus to form the typically small-diameter, "undistinguished" efferent arteriole (Fig. 5).

The electron microscope, which provides tremendous magnifications approximating 50,000 to 100,000 diameters,* reveals that the glomerular capillary wall has a unique, complicated fine structure which forms the filtration apparatus. A diagrammatic schema compiled from electron micrographs by Hall[34] shows the relationship of

* For use in biology. Good resolution at 10^6+ diameters have been obtained in crystallographic studies.

structures forming the filtration apparatus of the glomerular capillary wall (Fig. 6). These relationships are better visualized in a three-dimensional conception (Fig. 7). The layers of this filtration apparatus, proceeding from the outer to the inner surface of the capillary, consist of (1) a large enveloping cell, the podocyte, which contains pseudopod-like projections, called trabeculae, which end in closely interdigitating pedicels (little feet). The slit-pores formed by the adjacent surfaces of pedicels approximate 100 angstroms near their basal surface. Thus the pedicels become living molecular

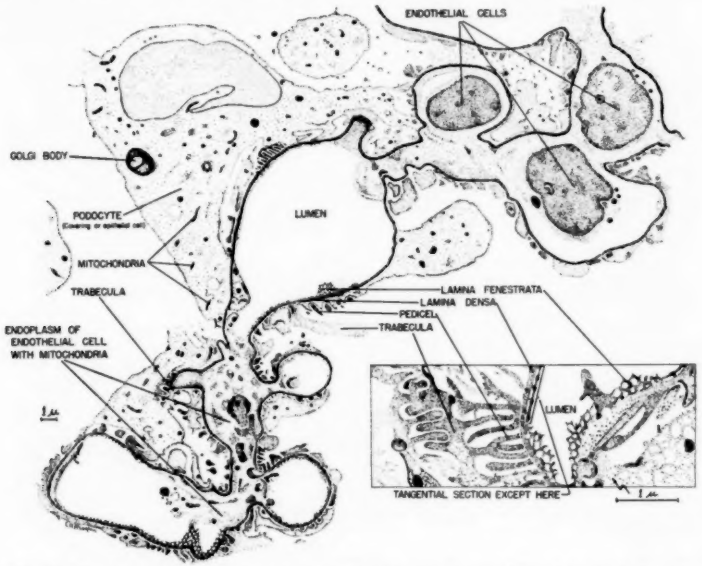


Fig. 6. This sketch of a section through the glomerular capillary is intended to show the relative size of the podocyte endothelial cell and the structural aspects of the capillary membranes. Recent improvements in technique allow somewhat better visualization of structural relations than is provided by this illustration, made some years ago. Under the light microscope the basement membrane of the glomerular capillary appears in sections as a relatively thick (0.3 to 0.5 micron) continuous, homogeneous membrane, which is revealed by the electron microscope to be composed of 3 intimately related structures: (1) Lamina fenestrata, forming the luminal surface, the thin (about 300 angstroms), highly porous membrane with nearly 5×10^9 openings per square centimeter about 900 angstroms in diameter, and earlier called "lining network." (2) Lamina densa, the continuous, dense middle layer of the glomerular capillary wall around 600 to 800 angstroms thick. (3) Pedicels, fine interdigitating processes from the podocytes (covering cells) on the external surface of the lamina densa. It is estimated that a podocyte may easily possess 2000 or more pedicels and perhaps hundreds of trabeculae. (Published through the courtesy of B. V. Hall.)

filters small enough to prevent passage of protein or other particles having a larger diameter. Hall calculates that if all the slit-pores in the glomeruli of the kidney were placed in a straight line end to end, they would extend for 2000 to 4000 miles![35] The pedicels "stand on" (2) a thick, relatively dense membrane, the lamina densa. The lamina densa appears to be the definitive "basement membrane" seen under the light microscope. The lamina densa (0.08 to 0.12 millimicron thick) originally was thought to have many minute pores penetrating it. More recent studies suggest that these "pores" were fixation artifacts. The membrane is thought to consist of a hydrated

gel continuum formed by free and protein-complexed polysaccharides. The lamina densa is lined by (3) the innermost layer of the glomerular capillary wall, i.e., "filtration apparatus," which is a perforated endenchymal (endothelial cytoplasm) membrane called the lamina fenestrata. This thin (0.04 millimicron) membrane cannot be visualized with a light microscope. It has a more or less sievelike structure. Between some endothelial cells porelike structures have been observed, sufficiently small to restrict passage of plasma proteins to the basement membrane.

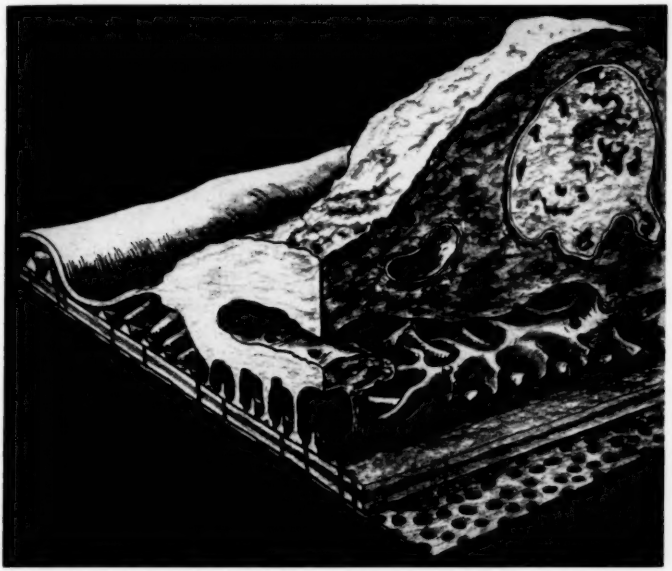


Fig. 7. Schematic drawing of a podocyte with trabecular processes ending in pedicels which cover the external surface of the effective basement membrane, the lamina densa. The thin lamina fenestrata is the bottom layer. The reconstruction was made from photomicrographs of material which originally contained several fixation artifacts. These included excessive shrinkage of the pedicels causing an apparent broadening of the interdigital spaces between pedicels; and holes in the lamina densa which were originally interpreted as pores, but which cannot be demonstrated by newer, better fixation techniques. (Reproduced through the courtesy of Dr. Hans Elias.)

Current information permits only reasonable speculation about the process of filtration. Plasma entering the afferent arteriole presumably is distributed promptly through the several ramifications of this vessel. The rather abrupt bifurcations at almost right angles to the entering channel may provide a mechanism by which separation of cellular from fluid elements takes place—a "skimming" phenomenon.[66] The plasma is sieved through the nonselective gel-like substance of the lamina densa. Presumably molecules soluble in the gel phase, including water, albumin and small particles such as glucose, urea and electrolytes, pass through the membrane and between the narrow spaces formed by the closely interdigitated pedicels. Fluid and solutes then enter the trabecular spaces of Bowman's capsule. The function of these structures is not clear. The small slit-pore between pedicels prevents entry of albumin unless that cigar-shaped molecule happens to enter head-on. The pedicels of the trabeculae might govern net passage of fluid through the lamina densa by obstructing some surface areas, rendering these sites impenetrable. In this way net filtration would have to take place only in

those areas not covered by pedicel protoplasm. It is not possible at this time to exclude a more active transport role of the pedicel for water and solutes.

From the functional viewpoint glomerular filtration may be altered to the same extent by different processes which interfere with either the porosity of the lamina fenestrata or the molecular structure of the lamina densa; or with the interdigitated areas covered by the pedicels; or with the actual numbers of pedicels; or with patency of the trabecular spaces; or following injury to the pedicels or podocyte itself. It seems conceivable that temporary distortion or change of the interdigitations of the trabecular pedicels, following some change in the podocyte protoplasm, could reversibly alter the passage of fluid and solutes through the filtration membrane.

The Tubule

Reabsorption of the bulk of filtered solutes occurs in the proximal tubule by some energy-determined phenomena, according to current concepts of renal physiology. Transport of ions, with isosmotic quantities of water in this segment of the tubule, must occur by somewhat different regulatory processes than those more flexible ones envisioned for the distal tubule. Architectural features facilitating bulk transport of ions have been suggested by electronmicrographs of tubule cells from the mouse kidney. Rhodin has demonstrated that the proximal tubule cell consists of densely packed microvilli extending into the tubule lumen, but originating in the cell cytoplasm.[76] There appear to be small pores at the base of the microvilli which terminate in coiled invaginations in the surface membrane of the cell. Certain granules and vacuoles within the cell substance presumably represent secretion products. The cells contain a Golgi zone near the nucleus which is concerned with intracellular activities, and organelles, called microbodies. These may be precursors of the mitochondria. Occasionally they enlarge, form intracellular hyaline bodies and burst through the cell into the tubular lumen to form a hyaline cast. The mitochondria contain about 90 per cent of all enzymes in the tubule cells and presumably are the source of most intracellular energy reactions. Rhodin believes that most of the water reabsorbed by the proximal tubules probably enters the cell through the cell membrane covering the microvilli. Passage through the cell is facilitated by cogwheel-like lamellations of the membrane on the basal surface of the cell. The diffusion surface is thereby tremendously increased. The orientation of mitochondria within the basal lamellar folds and their change in fine structure during certain reabsorptive processes are consistent with a possible active role in energy or transport phenomena. As in the glomerulus, it is obvious that disturbance of either orientation or fine structure of the cell or its appendages could modify tubular functional processes.

CURRENT CONCEPTS OF RENAL FUNCTION

General Considerations of Filtration Rate

Renal physiology has now advanced beyond the antediluvian era (before 1956, according to Homer Smith[85]) and is concerned with the consequences of discrete renal functions, rather than the comparison of simple measurements like glomerular filtration or renal plasma flow per se. However, interpretations of the measurements of filtration rates and urinary excretions of water and electrolytes underly most inferences about renal regulatory processes. The quantities of excreted water and salts, such as sodium and chloride, rarely exceed more than 10 per cent of the amounts filtered. Hence minor changes in apparent quantities filtered could account for relatively enormous changes in quantities reabsorbed or excreted. For example, an error of 1 cc. per minute

in estimate of the glomerular filtrate formed would be equivalent to an error of 1.4 liters of filtrate formed per day. This quantity of filtrate would contain approximately 225 mEq. of sodium, equivalent to 1.4 liters of extracellular fluid. Inferences about the capacity of tubule cells to reabsorb sodium, based upon the quantity of sodium excreted, would be in considerable error if the significance of small variations in filtration rates were not properly appreciated. Wesson has detailed other major errors contributing to inaccurate interpretation of studies based on clearance measurement.[102] For example, estimates of glomerular filtration rate from endogenous creatinine clearances may be satisfactory, provided serum creatinine is determined accurately,[36, 47] extensive renal damage is not present,[86] and urine collections are complete and timed properly.*

To evaluate the significance of reported filtration rate measurements when these are related to sodium chloride reabsorptions, Wesson suggests that the following be considered: (1) experimental protocols using constant infusion of inulin with bladder washing; studies having at least three control and test periods and proof of the constancy of plasma concentrations are more reliable than studies lacking one or more of these. (2) When plasma composition changes, the possible effect of such change on salt excretion must be evaluated. (3) Excretion of chloride is a more reliable index of salt reabsorption than is that of sodium, since interpretation of the latter necessitates quantitation of various cationic exchange systems. (However, it is possible that anion exchange systems also exist!) (4) Data obtained in rapidly changing states are less reliable than those obtained when filtration rate, urine flow and plasma composition are changing slowly or not at all. (5) A reasonable relationship of load to excretion should be evident. Suspicion should attend hypotheses predicting that the absolute magnitude of excretion varies directly or in constant proportion to tubular (filtered) load, or when concentration and volume may be used interchangeably as factors determining the tubular load.

Further, in evaluation of physiologic data, it should be recognized that:

1. Filtration rate usually changes in the presence of acute changes of sodium chloride excretion (especially in the dog). Osmotic loading and use of specific tubular inhibitors or stimulants are exceptions.

2. Change in filtration rate, as a tubular loading factor, usually may be considered sufficient cause for observed acute changes in sodium chloride excretion. Under such circumstances the contribution of tubular "reabsorption" of filtered solute is usually a less important contribution quantitatively.

* The major error in clinical clearance measurements does not occur in the laboratory. It usually results from improper timing of collection periods and small, incompletely voided urine samples. Properly, a collection period should begin exactly at that minute the bladder is emptied (the prestudy urine being discarded) and is terminated after at least one or more hours when the bladder is emptied again. The time of voiding is recorded. At least 2 periods are required. A sufficient urine volume is ensured by producing a mild diuresis with ingested water (approximately 10 cc. per kilogram for children). If bladder emptying is complete and the time of such emptying is accurately recorded, the periods can be of any length. If small urine volumes are expected, each period should be at least 8 to 12 hours long. By recording the time when a blood specimen is obtained at the beginning, at the end of the first and again after the second period, the urine collections can be "bracketed," the blood midpoint determined by extrapolation and "false starts" avoided. If the urine collection periods are only 1 to 2 hours long and the patient can be counted on to void at approximately the intended times, a single midpoint blood specimen will suffice. With protracted collection periods the patient need not fast.

3. The regular association of filtration rate changes with acute excretion rate changes is applicable to diseased as well as normal kidneys.
4. Filtration rate changes alone are quantitatively sufficient to account for chronic changes in excretory rates.
5. Lack of correlation between filtration rate and excretion may suggest technical errors such as dead space or collection inadequacies, rapidly changing inulin clearances from period to period, or a rapid change in any other factor maintaining a steady state.

General Considerations of Tubular Functions

Clinical patterns of tubular dysfunction have recently been analyzed by Mudge.[60] For example, the "overflow type" of increased urinary excretion of a substance is not a primary tubular defect, but is associated with an extrarenal disturbance giving rise to abnormally high plasma levels. Although total excretion may be increased, renal function may be considered unimpaired if the clearance of the substance $\left(\frac{UV}{P}\right)$ is unchanged. However, the most common type of relationship encountered in human beings is a change in renal clearance with an associated change in total excretion. These usually represent a defect in renal function, since in most instances the normal renal tubule responds to a change in plasma concentration and hence in filtered load by similar directional change in renal excretion. Increased clearance might result from an increase in the amount excreted (UV) or from a decrease in plasma concentration (P) or from a combination of both. Renal clearance may increase without change in the rate of total excretion if plasma concentration decreases. Similarly, clearance may decrease if UV decreases relative to P.

Tubular transport of sodium and chloride is conventionally defined as the removal of these ions from the filtered load passing down the tubular lumen. Mudge considers that this transport presumably takes place across the tubule cell and into the peritubular interstitial fluid or plasma, and requires energy. The energy-linked intracellular phenomenon associated with the process of ion transport determines the reabsorptive or secretory capacity of the tubular cell, depending upon the direction in which the process is oriented. Load is of course a function of plasma concentration of the substance, the extent of its binding to plasma proteins and the filtration rate. The quantitative relationships determining maximal rates of tubular transport require that several conditions be met. First, the nephron population must be homogeneous to the extent that transport would be proportional to load in any single nephron at any transport level below the maximum. As the amount available for reabsorption is increased, some point is reached at which the cell transport capacity is saturated (T_M), and beyond this level further increase in load yields no further increase in tubular reabsorption or secretion, the excess being excreted.[87] In general, the reabsorptive capacities of tubules differ. The degree to which

the transport capacities of nephrons within a single kidney differ are evidenced by the so-called splay in the titration curve of substances having a maximal rate of tubule transport. In addition to possible heterogeneity in structure of the nephron population, variations in the kinetic components within the cell will alter the titration curves, both for individual nephrons and for the kidney as a whole. The problem of tubular transport is an important one and underlies all attempts to evaluate the altered rates of excretion of substances relative to their filtered loads.

The diversities of structure, perfusion and function of the nephron population have recently been theoretically considered by Bradley and Wheeler.[11] As demonstrated by dissection, within a given kidney nephrons may differ greatly in dimension, in configuration, in construction and in arrangement.[62, 63] The differences are exaggerated in renal disease. Circulatory adjustments within the glomerulus may result in a partial and nonuniform reduction in filtration in some glomeruli as compared to others, and therefore in perfusion of certain tubules. Disease or injury affecting the kidney may induce hemodynamic as well as tissue derangements. It is obvious that interpretation of change in renal function attributed to either physiologic or disease processes must be made with careful consideration for such variations.

MATURATION OF RENAL FUNCTION

Within the last 10 years measurements of renal functions such as glomerular filtration, renal blood flow and tubular transport capacities were extended to newborn and older infants. The results obtained suggested that these parameters of function in the young infant were much reduced compared to adult normal standards, when based on either body weight or surface area.[109] Surface area is usually considered better for evaluation of most metabolic functions; however, it may not be applicable to kidney function in the infant whose surface is very large relative to mass. Infant's kidneys retain some fetal characteristics, yet seem to regulate body composition with admirable precision, considering the rather unique, dilute diet consumed. As McCance pointed out, clearly the effectiveness of renal function should be evaluated according to the purpose it serves.[50] Since the composition of body fluids is maintained at reasonably constant levels in the infant just as in the adult, renal function must be effective despite its apparent degree of "reduction." McCance suggests that a possible resolution to this paradox may be achieved by relating values for discrete renal functions, such as glomerular filtration rate, to the total body water content. Friis-Hansen suggests that the volume of extracellular fluid would be a still better common denominator for comparing glomerular

filtration, e.g., of an infant with that of an adult.[22] He suggests that the reason why a close relationship has been found between renal function and surface area may depend on the parallel changes of surface area and extracellular volume and the dependence of renal function on the latter. The results obtained by using these different frames of reference with respect to glomerular filtration are shown in Table 6. It is evident that interpretation of filtration rate based upon the volume of total body water which it regulates defines a functional capacity in the infant which is at least equivalent to that of the older

TABLE 6. *Glomerular Filtration Rate* during First Month of Life*

AGE IN DAYS	NUMBER OF INFANTS	WEIGHT (KG.)	SURFACE AREA (M.²)	GLOMERULAR FILTRATION RATE			
				Obs.	Per M.²	Per L. TBW†	Per L. ECW†
2-4	9‡	2.8	0.21	3.7	18.4	1.8	3.3
7-14	14	2.7	0.20	5.2	26.6	2.7	5.2
15-21	7	2.8	0.20	5.4	27.0	2.7	5.8
Adults	–	70.0	1.73	120.0	75.0	2.86	9.52

* Determined as mannitol[78] or inulin clearance.[1,19]

† Calculated from data of Friis-Hansen,[22] where

TBW, 0–11 days = 77.6% body weight
ECW, 0–11 days = 41.6% body weight
TBW, 11 days–6 months = 72.2% body weight
ECW, 11 days–6 months = 33.7% body weight

where S = GFR/V.D. Average values of 0.25%/minute and 1.10%/minute for slope (S) obtained in 4 infants 1 day old and 4 infants 1–30 days, respectively. Adult values = 0.69–1.3, average 1.0%/minute.

‡ Excluding 6 infants studied by Dean and McCance, average values were as follows: GFR, 4.70; GFR/square meter, 26.0; GFR/liter, TBW, 2.65; GFR/L., ECW, 4.94

child or adult. Possibly, during the first days of life, transitional inadequacies may appear. In this period extraordinary demands on renal adjustment may exceed the capacity of the kidney, functioning at nearly maximal levels, to respond further.

Inability of the premature or newborn infant to elaborate a urine having a concentration greater than 800 milliosmols per liter has often been considered a manifestation of immaturity or functional inadequacy of the infant kidney.[2, 38] The older child or adult can elaborate approximately twice as concentrated a urine (1400 to 1600 milliosmols per liter) under similar stress. Since the infant responds to water loading and to exogenous vasopressin injection [3, 15] almost as effectively as the older subject does, the primary ability to dilute or concentrate the urine obviously is present. Analysis of this function with reference to body composition suggests that the "osmostat" may be set at a different level to serve better in regulation of the changing body composition. Recent data suggest an increase of water relative to solids in the

newborn period.[22] The volume of extracellular and intracellular fluids constitutes nearly 80 per cent of body weight in premature and newborn infants. Volumes progressively decrease to an asymptote where they comprise only 60 per cent of body weight as the infant reaches 6 to 12 months of age. The extracellular fluid is the larger component of the expanded total body water in the newborn. The dilution studies of body distribution are consistent with direct observations on tissue (muscle and skin) composition in the infant.[54, 55] Since skin comprises approximately 15 to 20 per cent of total body mass and contains over 30 per cent of the total extracellular fluid in the young infant,[84] decrease in its water content with age probably accounts for the reduction in volume of the total extracellular phase as estimated by vivo-dilution techniques.

TABLE 7. *Partition of Outgo of Sodium, Potassium and Nitrogen in Values per Kilogram per Day**

	PERIOD	INTAKE	URINE	STOOL	INSENSIBLE	TOTAL
Sodium (mM.)	I	3.74	2.28	0.26	0.89	3.43
	IV	4.98	4.02	0.42	0.30	4.74
Potassium (mM.)	I	5.94	4.01	0.43	0.98	5.43
	IV	6.72	5.56	0.50	0.60	6.66
Nitrogen (Gm.)	I	0.75	0.33	0.14	0.11	0.58
	IV	0.98	0.61	0.12	0.13	0.86

* Infant D.S —period I, age 1 month, weight 3.05 kg.; period IV, age 4 months, weight, 3.45 kg.

The process of concentrating intracellular as well as extracellular solute can be achieved in the newborn period only by elaboration of a dilute urine. Retention of mineral and water in isotonic quantities as a result of the load provided by dilute cow's milk, for example, would require further expansion of total body water and excretion of a dilute urine to preserve solute concentration. With increased mineral load further weight gain (as extracellular fluid) occurs. Such a phenomenon was observed by McCance and Widdowson in studies of solute-loaded piglets.[51] Since the infant's feed provides a large quantity of dilute fluid relative to the solute it contains, homeostasis can be served only through elaboration of a dilute urine. Thus, in the broadest view, the concepts of teleology need not be eschewed, and the regulation of water and solute concentration by the infant kidney seems reasonably well adapted to the needs they must service. Perhaps the arbitrary standard of reference chosen by the investigator or clinician is more at fault than the regulatory capacity of the infant kidney.

The normal infant's kidney regulates excretion of electrolyte to provide retention sufficient to sustain growth. When a normal cow's milk formula is fed, the partition of outgo indicates the precision of renal

TABLE 8. *Average Daily Water Balance, Urine Organic Acid and Solute Concentration in a Fasting Infant*

AGE	PERIOD AND GLUCOSE INTAKE	DAYS	WEIGHT, FINAL (KG.)	WATER BALANCE (KG./DAY)			SERUM [Na] (mM./L.)	URINE	
				Intake	Urine	I.I.		[R-]* mEq./L.	[SOLUTE] mOsm./L.
1 month	Fore†	10	3.249	379	254	48	146	20	378
	Fast	5	2.925	201	132	42	133	57	409
2 months	Fore†	10	3.490	581	282	58	142	22	418
	1 gm./kg./day	5	3.113	180	48	54	141	104	854

* Organic acid concentration.
† Control period on usual evaporated milk formula.

adjustment (Table 7)[24] and suggests the relative magnitude of extrarenal water losses.

Regulation of the tonicity of body fluids during fasting in a young growing infant requires conservation of ample quantities of water, retention of sodium and potassium in quantities sufficient to sustain the

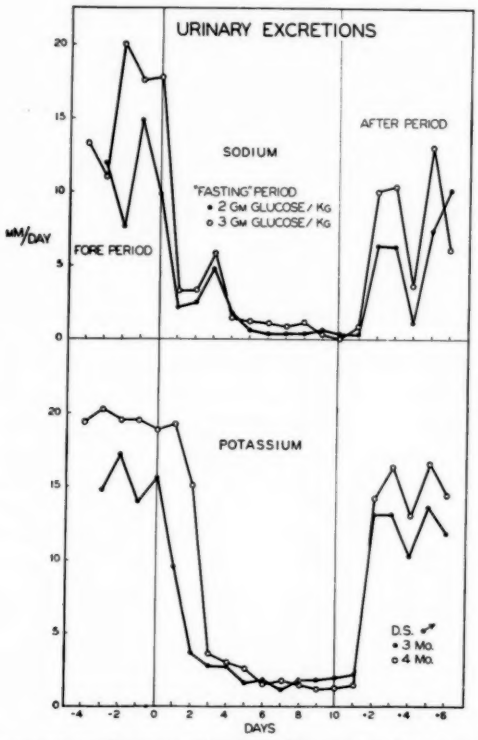


Fig. 8. Note prompt renal conservation of sodium and potassium when intake of these ions is omitted and limited calories are provided by oral glucose in a young infant.[24]

integrity of the extracellular and intracellular fluids which they define, and removal of those solutes which accumulate during the catabolic phase. This provides a "difficult piece of regulation for an inexperienced kidney" (J. L. Gamble).

Limitation of concentrating capacity at 1 month of age in one infant obligated excretion of most of the water available from intake and tissue sources and not committed to heat regulation through evaporative (insensible) loss.[24] The observed dilution of the body fluids indicates that what was called for was excretion of an even more dilute urine. But perhaps overshooting the mark in defense of body composition may be permitted such a young kidney. With further experience and provision of 1 gm. of glucose per kilogram per day during the fasting period in an endeavor to restrict utilization of body protein to meet energy requirements, the nearly optimal renal concentrating capacity for infants of this age permitted removal of similar quantities of solutes in somewhat less than half as much water (Table 8). When 2 or 3 gm. per kilogram per day of glucose with ample quantities of water provided calories, but with exclusion of all other solute intake, the electrolyte composition of the body fluids was sustained effectively by an alert response of the kidney to successfully limit urinary excretion of the major cations of the extracellular and intracellular fluids, sodium and potassium, respectively (Fig. 8). The virtually complete retention of sodium when intake of this is negligible had been demonstrated in adults many times. Prompt renal retention of potassium in defense of intracellular composition is rather surprising, particularly since the adult kidney sluggishly restricts urinary potassium loss in the absence of intake.[9, 20] In this particular infant 1 to 3 gm. per kilogram of glucose daily as the only source of calories or solute also served to minimize the urinary losses of solute incidental to fasting (Fig. 9). The response was not as effective as that observed in

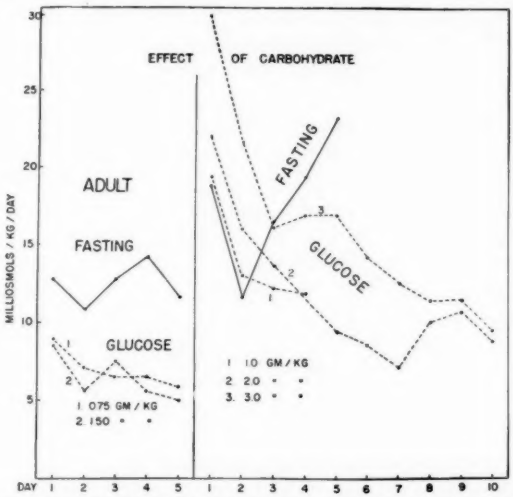


Fig. 9. Comparison of the effects of fasting and various levels of glucose intake during fasting upon total solute excretion in the urine. The reduction of urinary solute excretion in the adult has been described previously.[25] Infant D. S. was 1, 2 and 3 months of age, respectively, during the fasting period and subsequent observations with increments of glucose providing the only solute intake. The reduction in total solute excretion was a consequence of diminished excretion of nitrogen and organic acids characterizing the effect of glucose during the fasting period.[24]

adults under somewhat similar circumstances.[25] One service of glucose is evident from the reduced solute excretion achieved by diminishing cellular protein catabolism with gradual decrement in the nitrogen and organic acids claiming excretion in the urine.[25, 26] Since body water in the infant is large relative to content of the structural ions sodium, chloride and potassium, excretion of water from which these ions had been extracted effectively maintains body composition, and the precision of renal regulation becomes apparent.

Since the enzymatic content of tubular cells presumably is genetically determined, it would be reasonable to suppose that even premature infants normally have appropriate quantities of tubular cell enzymes. The pattern and quantity of amino acid excretion by young infants differs from that of older children or adults.[92] It seems likely, therefore, that either the pathway for utilization or excretion of the substrate or end product of the enzyme interaction may be different in very young infants than in older ones. Some enzyme systems are known to be intact, however. The response to bicarbonate infusions and carbonic anhydrase inhibitors, for example, indicates that the carbonic anhydrase system is present and functioning with expected efficiency.[97]

It is evident that the influences of body composition and of load relative to excretion require better definition before deviations from the adult patterns of urine excretion by young infants can be ascribed properly to "immaturity" of kidney function.

CONCENTRATION OF THE URINE

Physiology

Concentration or dilution of the urine is the major process by which regulation of the body fluids is achieved. This mechanism may be thought of as a fine adjustment which brings into focus those phenomena which maintain constancy of the body fluid volume and concentration during grossly variable intakes and extrarenal losses of fluid and solute. Only two basic tubular mechanisms seem needed for production of concentrated or dilute urine from isosmotic glomerular filtrate:[4] (1) active sodium and chloride transport, with variable membrane permeabilities to salt and water arranged in a definite sequence along the renal tubule; and (2) a regular, consistent organizational pattern of the renal tubule anatomically, within the kidney itself. Although specific information about the details of active transport systems for electrolytes in the renal tubule are lacking, that such transport systems must exist is evident from the work of Bott and associates[10, 100] and of Solomon et al.[93] The latter investigators quantitated the flux of sodium across the renal tubular epithelium of necturus by micropuncture studies. Direct measurements indicated that this process met the requirements of an active transport system.

Since sodium and its anion equivalent are responsible for most of

the osmotic pressure of the glomerular filtrate, the process by which sodium (plus anion) is removed from the tubule lumen accounts for the formation of *either* dilute or concentrated urine; however, the *extent* of dilution or concentration of the urine is dependent on the removal of water, since, at either extreme, urine may contain the same total quantity of solute. Careful analysis of osmotic pressure in tubular fluid obtained by micropuncture led Wirz to postulate an ingenious

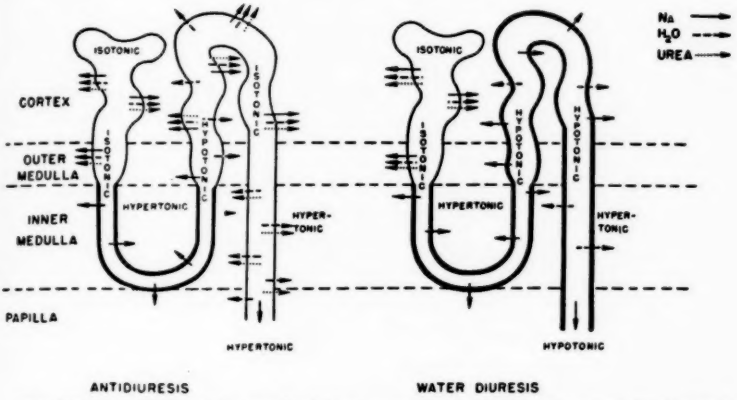


Fig. 10. A summary of the renal tubular processes involved in the concentration and dilution of the urine. Water-permeable segments of the nephron are drawn with light lines and impermeable segments with heavy lines. The arrows do not have quantitative significance; they indicate only the direction and location of sodium salt, urea, and water movement. Note that tubular events in the dilution and concentration of the urine are qualitatively the same up to the distal convoluted tubule. Fluid entering the distal tubule in the inner medulla is reduced in volume, but isosmotic. The loop of Henle is considered water-impermeable, and active sodium transport occurs from it into the medullary structure. In antidiuresis the distal tubule and collecting ducts are relatively water-impermeable, hypotonicity of the fluid entering the distal tubule is reduced by the osmotic gradient in the cortex, and greatly reduced quantities of isotonic fluid enter the final segment, where water is removed because of the hypertonicity of the interstitial medullary fluid. During water diuresis the distal segment and collecting ducts are considered relatively impermeable to water, and except for active sodium reabsorption in the distal tubule and some isosmotic reduction in volume of the urine, a large dilute urine is excreted. (Reproduced through the courtesy of R. A. Berliner and editors of the *American Journal of Medicine*.[4])

concept of "countercurrent flow" within the renal medulla.[106] This important contribution provided a model which satisfied most of the requirements for a urinary concentrating apparatus. The original concept of Wirz was subsequently modified[107] and refined further by Berliner and associates,[4] as illustrated in Figure 10.

The general features of this process may be described as follows, according to Berliner et al.: After filtration, water is presumed to move passively out of the tubular

lumen as a result of an osmotic gradient created by the active transport of sodium.* Walker, Bott and associates[100] showed that the concentration of solute at the end of the proximal tubule remained isotonic to plasma. This appears to be the case even though water diuresis is being observed in the animal under study.[108] Since the quantity of fluid leaving the proximal tubule is only about 15 per cent of that entering it at the glomerular end, the greater portion of the sodium salts must be removed from the tubule in this segment and be associated with passive, isosmotic diffusion of water through a highly permeable tubular membrane. The reduced quantity of isotonic proximal tubular fluid (15 ml. per 100 ml. of glomerular filtrate) then enters the loop of Henle. No direct observations on events occurring in this portion of the loop are available, but elaboration of hypotheses concerning the events in this segment of the tubule are the current fashion. Since the fluid entering the first part of the distal convoluted tubule after emergence from the loop of Henle is considerably hypotonic to plasma (by micropuncture studies), it is apparent that sodium salts must be reabsorbed from the fluid coursing along this portion of the nephron without an equivalent quantity of water. The epithelium of the loop, therefore, is assumed to have a low permeability to water which is not modified by antidiuretic substances (ADH) secreted by the neurohypophysis. The transported sodium salts accumulate in the interstitial fluid of the medullary tissue surrounding the loop and attain a concentration hypertonic to that of the intraluminal fluid. The mechanism by which this concentration of solute occurs is best explained on the basis of a "countercurrent exchanger" system.

An analogy with the countercurrent exchange of heat in a U-shaped hot water heating system is useful in this regard.[4] For example, visualize a pipe bent in the middle and reflected upon itself. Except for the sides which are in direct apposition to each other, the pipe is insulated from the surrounding area. Fluid circulates through the pipe, entering it at the rate of 10 ml. per minute and emerging at the same rate. Application to the bend of the loop of a heat source yielding 100 calories per minute would warm the entering fluid from an initial temperature of 30° to one of 40° C. adjacent to the heat source. In a straight tube the heat then would be dissipated to an extent dependent on the rate and distance of flow and the temperature of the environment. A localized heat source confined to the central area of such a straight tube would prove relatively inefficient. In the bent tube with adjacent loops, however, the heat would be dissipated as flow continued up the ascending limb of the pipe because of heat transference to the colder fluid flowing down the descending, entry limb; thus the entering fluid would be preheated before reaching the heat source. Gradually a new equilibrium would be reached as the temperature of inflow water rose, boosted further at the heat source to gradually yield water emerging from the ascending pipe at progressively higher temperatures.

By analogy, the same principle may be applied to the concentration of solute in the urine of the reflected limbs of Henle's loop or in the plasma of the reflected capillary loop of the adjacent vasa recta. Thus as sodium enters the interstitial fluid surrounding Henle's loop the interstitial concentration of salt would continue to rise only if the tubular epithelium was impermeable to water and as long as the tubular fluid contained sufficient solute which could be absorbed. Reabsorption of solute (essentially sodium and anion) would continue only as long as a chemical or electrochemical gradient permitted movement of sodium from the lumen into the interstitial fluid. At equilibrium no further sodium would be transported, and therefore further dilution of the lumen contents would not occur. The sodium gradient from lumen to interstices

* The possibility of an "osmotic diffusion pump," postulated by Franck and Mayer,[21] which consisted of cyclic polymerization of small molecules incorporating water at one surface of the cell and their depolymerization yielding water at the opposite surface, has been considered thermodynamically inadequate to account for the concentrating function of the kidney.[12] It has not been possible to refute the concept of a water "pump,"[77] but the same end could easily be attained by an alternative explanation based on solute transport. Explanation of the concentrating operation is more easily achieved if it does not involve movement of water against osmotic gradients.

could be maintained by at least two factors: the characteristics of the medullary blood flow, and localized impermeability of the tubular epithelium to water.

The countercurrent principle applied to the vasa recta which course adjacent to the loop of Henle implies that some of the salt in the interstitial fluid would enter them. Gradually the concentration of salt in the capillary would increase until the emerging plasma would have a higher salt concentration than that entering the capillary loop. Thus some of the sodium would be carried away from the interstices, preserving the gradient and permitting further transport of sodium out of the luminal fluid. However, if flow in the capillary loop were sufficiently rapid, an increase in the concentration of salt in the capillary blood flow would occur at the expense of luminal fluid salt concentration. There are no estimates of the rate of blood flow in the vasa recta, but on the assumption that this rate is slow because of viscosity and the countercurrent flow, the final concentration achieved in the urinary fluid entering the distal tubule would be inversely proportional to the square of adjacent blood flow.

The fluid emerging from the loop of Henle into the distal tubule is hypotonic to plasma and diminished in volume. It is reasoned that hypotonicity of this fluid occurs irrespective of whether a final hypertonic or hypotonic urine is to be elaborated. Fluid leaving the loop of Henle within the medullary area of the papillae enters the distal tubule in the outer medulla where interstitial salt concentration is somewhat less; i.e., the gradient is reduced. ADH is thought to maintain permeability to water of the cell membranes in the distal tubule and collecting ducts. With high concentrations of ADH, permeability to water is increased and water diffuses into the interstitial areas. The diffusion of solute dissolved in water would depend upon the gradient involved. In the cortical area of the kidney lobule ADH would facilitate diffusion of water and solute from the distal convoluted tubule until isotonicity between luminal fluid and that of the interstitial tissue was established. A greatly reduced volume of isotonic fluid would then enter the collecting duct. As the urine in the collecting duct again passes down through the hypertonic medullary area, water could escape until the osmotic pressure of the urine equaled that of the surrounding interstitial fluid. A fraction of the urinary urea also enters the interstitial fluid from the collecting duct and contributes to the hypertonicity in this area. This terminal withdrawal of water and small amounts of solute leads to elaboration of a maximally concentrated urine.

In the absence of sufficient quantities of ADH the membrane of the distal and collecting tubule remains relatively impermeable to the passage of water, but does not restrain slight further transport of solute. Instead of a reduced volume of isotonic urine entering the final collecting duct segment, most of the fluid which entered the distal tubule continues its course into the final segment. Since the epithelium of the collecting tubule also would be impermeable to water in the absence of ADH, no further water would be extracted on passage through the hypertonic medulla. The net result would be a dilute urine.

In this concept it is essential to recall that elaboration of urine represents a spectrum ranging from very dilute to very concentrated, rather than descriptive extremes. The direction and approximate magnitude of factors affecting the concentration of the urine were visualized by Berliner[4] according to the following relationship:

$$\text{Uosm} = \text{F}\left(\text{Posm}, \triangle\ \text{T}^{1}_{\text{NaCl}}, \alpha, \frac{1}{\text{V}^{n}}\right)$$

Where *Uosm* is the osmolarity of the urine; *F* represents fluid of the glomerular filtrate; *Posm* is the osmolarity of the arterial plasma; $\triangle\ T^{1}_{NaCl}$ is the change in net transport of sodium salts by loops of Henle, depending upon the concentration achieved in the medulla and represents (T^{1}_{NaCl}—$T^{c}H_2O$ Posm); $T^{c}H_2O$ is the volume of water contributed by the urine as it passes through the medulla; α is a factor related to the length of the countercurrent system and the effectiveness of equilibration of inflowing and outflowing capillary blood with new surroundings; V is the volume of blood flow through the medulla; n is an exponent (approximately 1 or 2,) depending upon net sodium transport in the loops of Henle.

It is obvious that concentration of the urine may be conditioned by

the volume of glomerular filtrate and the rate at which it is formed. For example, reduction in glomerular filtration rate during maximal water diuresis reduces the extent to which the urine can be diluted, since it decreases the quantity of solute delivered to and entering the interstitial (papillary) concentrating area; in fact, a urine somewhat more hypertonic than plasma can be elaborated in the absence of ADH by this mechanism.[5]

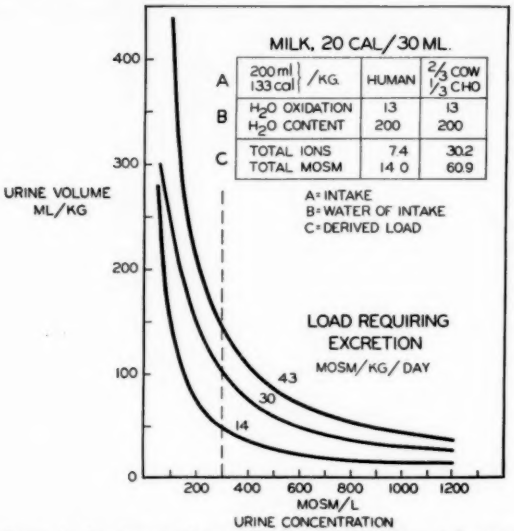


Fig. 11. Schematic drawing similar to those of Gamble[23] and Pratt.[70] The curves describe the relation $L^1 = UV$, where L^1 is load requiring excretion, derived from milk intakes noted in the chart; U is urine osmolality; and V is volume of urine in milliliters per kilogram per day. The dotted line indicates isosmolality with relation to extracellular fluid. Progressive increase in concentration of the urine from minimal osmolality to isotonicity defines the major contribution of antidiuretic hormone. Maximal concentration beyond 400 to 500 milliosmols per liter probably indicates the effect of the final concentrating operation in the collecting ducts.

The relative importance of ADH in water conservation rests upon the premise that it increases permeability to water in the distal segment of the nephron and thus prevents introduction of a large volume of dilute (hypotonic) urine into the final concentrating segment. Thus, even without the ultimate maximal concentration achieved in the final concentrating segment, ADH promotes the excretion of at least isotonic urine. The net effect on water economy is indicated by Figure 11.[70] If an infant requires excretion of 30 milliosmols of solute per kilogram per day in a very dilute urine having a concentration of 100 milliosmols per liter, approximately 300 ml. of urine would be elaborated. In an isotonic urine 30 milliosmols would be excreted in ap-

proximately 100 ml. of urine, a net saving of 200 ml. of water per kilogram.* Further concentration of the urine to 900 milliosmols per liter would reduce the required volume for excretion of solute to about 30 ml., a further saving of 70 ml. of body water. It is apparent that by increasing concentration from hypotonicity to isotonicity a larger quantity of water is saved than is achieved by a further threefold increase in concentration. It is equally obvious that the larger the solute load which requires excretion, the greater the relative saving achieved by elaboration of an isotonic or hypotonic urine rather than a dilute one. Further economy of water may be effected by excretion of a maximally concentrated urine. A corollary to this observation implies that reduction of solute load requiring excretion will conserve body water when the kidney is incapable of achieving maximally concentrated urine.

A useful physiologic concept which relates the tubular (filtered) load of solute to excretion of water has been formulated by Wesson and Anslow[103] and defines the tubular concentrating operation in quantitative physiologic terms. The osmolar clearance, designated *Cosm*, indicates the volume of filtrate water obligated by solute requiring excretion at its original concentration in the filtrate. It is expressed as

$$\text{Cosm (ml./min.)} = \left(\frac{\text{Uosm V}}{\text{Posm}}\right)$$

and ranges in volume from 1 to 3 per cent of the glomerular filtrate. When solute is removed from the urine without an equivalent amount of water (as in the final concentrating segment, the collecting duct system without ADH activity), excretion of this water freed of solute is designated "free-water" clearance, C_{H_2O}, where

$$C_{H_2O} \text{ (ml./min.)} = V - \text{Cosm}.$$

If, on the other hand, water is reabsorbed in excess of solute (e.g., in the distal concentrating segment with ADH and in the collecting ducts), the process is designated "free-water reabsorption," and *Cosm* numerically exceeds the urine volume; hence

$$T^c_{H_2O} = \text{Cosm} - V.$$

The details of this concept are clearly, simply and concisely described by Smith.[88]

Some Clinical Inferences

The countercurrent exchanger hypothesis for elaboration of a concentrated urine may explain certain clinical phenomena not readily interpreted otherwise. For example, malnourished infants with hypotonic dehydration often excrete copious quantities of dilute urine,[31] as if the activity of antidiuretic hormone were suspended. Infusion of strongly hypertonic solutions in quantities sufficient to raise osmotic concentration of extracellular fluid causes elaboration of a hypertonic urine without increasing the lowered filtration rate. C_{H_2O} is replaced by $T^c_{H_2O}$ in operational terms. If hyponatremia had been present in such an infant for

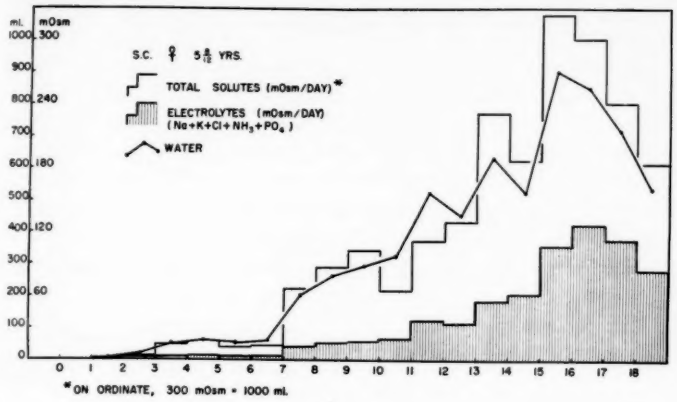
* In a young infant weighing 3 kg. there would be about 2.3 liters of body water. Therefore $\frac{3 \times 0.2}{2.3} \times 100 = 26$ per cent of body water conserved by this mechanism.

a long time and was associated with reduced glomerular filtration rate, both quantity of sodium available and the gradient for its transport across the loop of Henle and into the interstitial fluid would have been reduced, with resultant reduction in concentration of medullary interstitial fluid. Accordingly, less water would diffuse into the medullary interstitial tissue, and a greater relative volume of dilute urine would reach the distal tubule.

Failure to concentrate the urine in this segment need not imply inadequate antidiuretic activity, since high levels of circulating ADH were found by Heller in similar circumstances.[39] Presumably the large volume of water in the distal segment would limit influence of ADH, relatively small quantities of water would diffuse, and only moderate change in concentration of the fluid (from hypotonicity toward isotonicity) would occur. Reduction of the osmotic gradient across the collecting duct would further limit water extraction and prevent elaboration of a more concentrated urine. Therefore a dehydrated but hypotonic infant would excrete a relatively large volume of dilute or, at best, approximately isotonic urine. Infusion of a sodium load would increase the tubular load of salt and interstitial fluid salt concentrations and restore the intrarenal gradient in the medullary fluid, lesser amounts of hypotonic fluid would be delivered to the distal tubule, the effectiveness of ADH would be increased, less isotonic urine would reach the collecting ducts, and water would be extracted from them by the concentrated areas of the medulla, (i.e., increased $T^c_{H_2O}$). Excretion of a smaller volume of concentrated urine might be expected, and was observed.[56] Paradoxically, therefore, the solute load would lead to net conservation of water as tonicity of the body fluids was restored.

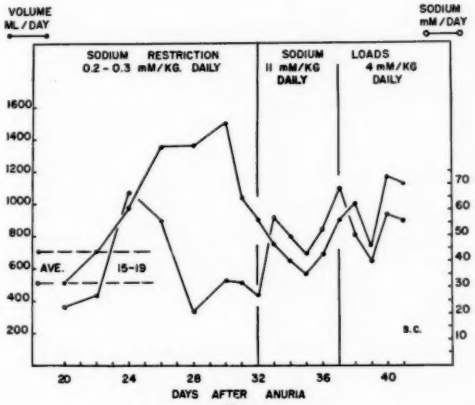
Another puzzling clinical situation relates to the isosthenuria of the early diuretic phase following anuria and the subsequent excretion of large volumes of dilute urine. Reference to the pathology of the nephron, body compositional changes, and inferences about modification in the countercurrent exchange of salt and water clarify the observations.

An illustration of the phenomena commonly observed is presented in Figure 12, A.[32] In the early diuretic phase total solute excretion becomes progressively larger and obligates an isosmotic quantity of water, determining urine volume. About one third of the solutes excreted are electrolytes, the major part of the solutes consisting of urea. Of the excreted electrolytes, half of these are cations, and about half of the cations are sodium, i.e., about one twelfth of the excreted solutes. In this patient, on the twentieth day following resumption of some renal function, the capacity to excrete a dilute urine was noted; however, the quantity of sodium excreted could not be altered appreciably either by dietary sodium restriction (0.3 millimol per kilogram per day) or loading (11 millimols per kilogram per day) relative to an average intake of 4 millimols per kilogram per day (Fig. 12, *B*). Similarly, water restriction failed to induce water conservation, although water loading produced the expected, but "blunted," response to yield a dilute urine. Administration of exogenous Pitressin at height of water diuresis reduced urine volume and concentration only to the preloading level (Fig. 13).



A

SODIUM EXCRETION vs. INTAKE AFTER ACUTE RENAL FAILURE



B

Fig. 12. A, Relative contribution of electrolytes and other solutes, principally urea, to the osmolarity of the urine in the early diuretic phase after 4 days of anuria attending acute glomerulonephritis in a child. Sodium excretion accounted for approximately half the urinary cations. The chart also indicates the isosmotic urine characterizing this diuretic phase.[32]

B, In the late diuretic and postdiuretic phase following anuria in this patient, sodium restriction did not markedly restrict sodium outgo, nor did a twentyfold increase in daily intake appreciably increase the excretion of sodium over the average levels found during the sixteenth to twentieth day after anuria or during the period of average intake 37 days after anuria. It is evident that sodium loads would lead to retention, while sodium restriction would lead to depletion of this ion as a result of the inability to restrict sodium outgo. For a possible interpretion of this phenomenon, see text. The increased urine volume observed from the twenty-fourth to thirty-second day was associated with an increased water intake.

As demonstrated by Oliver,[64] diverse portions of groups of nephrons must be involved in acute renal insufficiency due to severe circulatory derangements (in this particular instance, acute glomerulonephritis) in order to produce the clinical picture of "lower nephron nephrosis." After anuria some glomeruli would provide filtrate for tubules sustaining various degrees of damage and undergoing limited repair. The final urine and renal concentrating process would represent the resultant of these diversities. In general, a small amount of glomerular filtrate is formed per unit of time. In some nephrons all the filtrate would be reabsorbed in the proximal tubule; in others, none; with all

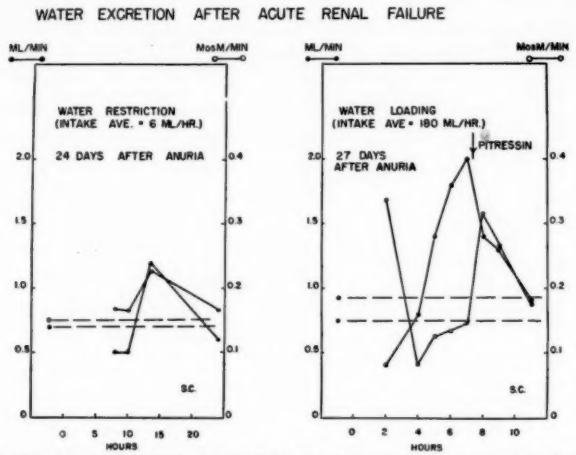


Fig. 13. Restriction of fluid intake fails to alter renal conservation of water or solute 24 days after anuria. Three days later, oral water loading produced a definite, but blunted, water diuresis, and the capacity of the distal tubule epithelium to respond to vasopressin was demonstrated.

degrees of variations in the remaining tubules. In general, small volumes of isotonic fluid might be expected to enter some loops of Henle. Here damage to the epithelium presumably might permit escape of some water, as well as salt, into the medullary interstitial tissue, accounting for the intertubular edema often seen in the renal papilla. Since sodium is excreted at a much lower concentration than obtains in the extracellular fluid and glomerular filtrate, some sodium must be removed at this level of the tubule, indicating that a gradient must persist in the loop of Henle. Similarly, potassium is excreted at concentrations 7 to 10 times that observed in extracellular fluid; hence considerable sodium must reach the distal tubule where sodium exchanges with potassium. The capacity of at least some tubule cells to secrete potassium must denote recovery of this important protective renal function.

Water restriction 24 days after anuria in our patient presumably enhanced neurohypophysial ADH secretion, but apparently the distal tubular epithelium was not sufficiently regenerated to manifest a detectable urine concentration response. Three days later some response to water loading and Pitressin was discernible, indicating the rapidity with which regenerative processes restored the capacity of the distal tubular epithelium to respond to ADH stimulation. Since the urine was only slightly hypertonic despite the ADH effect, it seems reasonable to suppose that the osmotic gradient deep in the medulla* had not been restored; therefore the final concentrating operation remained impaired. Complete regeneration following an ischemuric episode may take several months in children, but frequently is attained even after a severe, protracted period of acute renal insufficiency.

From the practical point of view, restriction of water or stringent restriction of sodium during early diuresis following anuria will lead to dehydration and sodium depletion. On the other hand, water loading to "wash-out" retained urea might further reduce interstitial osmolality, diminishing the osmotic gradient and limiting the concentrating operation still further. Coupled with reduced glomerular filtration, this might lead to sodium depletion and hypotonic edema. Obviously, good clinical management will provide an intake of salt and water just sufficient to meet continuing losses and maintain a progressive reduction of the total body water to normal volume.

Occasionally anuria is induced in dehydrated children without renal damage by excessive administration of intravenous glucose solution either without provision of salt or with infusion of hypotonic salt solution after administration of glucose. The sequence of events is not entirely clear. The most dilute urine contains solute at approximately 40 to 50 milliosmols per liter. Protracted excretion of a dilute urine would tend to maintain tonicity of the body fluids at normal levels, but ultimately would lead to hypotonicity if urine water and solute were replaced by intake of water† alone. As hypotonicity supervened, homeostatic functions of the neurohypophysial system and the kidney would come into conflict. Continued removal of water would further deplete solute, and even maximal retention of solute would not restore tonicity without the addition of exogenous salt. Ultimately faced with a circumstance requiring maximal *removal* of water to prevent further

* The situation appears to be somewhat analogous to that observed by Berliner[5] during unilateral circulatory impairment at the height of water diuresis in the dog.

† The glucose in glucose solution is either metabolized or induces a solute diuresis with further body solute depletion.

expansion of body fluids in defense of solute concentration, but repair of dehydration requiring *retention* of both water and solute, the perplexed kidney ceases to function, and anuria supervenes.

The clinical situation is more striking than, but similar to, observations made by McCance, who initiated relative oliguria in a salt-depleted subject by water loading.[52] In the clinical situation, administration of solute as dry salt or as a hypertonic solution will restore urine flow. Presumably, continued loss of solute and excessive administration of sodium-free water cause dilution of the medullary interstitial tissue concentrations of solute and simultaneously are associated with increased flow through the vasa recta. This process would continue to siphon solute from the luminal fluid and ultimately establish medullary tissue solute equilibrium at levels considerably below the initial value. As the solute concentration in the body fluids fell, and as body water increased, ADH excretion would be reduced. Membrane impermeability to water would lead to further losses of dilute urine.

At some point severe hypotonicity per se may lead to reduction in glomerular filtration by some mechanism which short-circuits the renal blood flow from the kidney [110] (Fig. 14). Reduction in the filtered solute load reaching the loop of Henle might then lead to anuria, since the flow of an extremely small quantity of fluid along the tubule would increase further transport of salt across the loop epithelium. Augmentation of the osmotic gradient for water, when the quantity of luminal fluid is small, would extract most of the remaining urine water from the collecting tubules as they coursed through the deep medullary tissues. The same effect also would be achieved if the loop of Henle were permeable to water. Infusion of solute in some way not yet understood serves to restore filtration, tubular load, luminal fluid flow and urination. Obviously this explanation is incomplete, since the complicated interrelationships between the neurohypophysial system, volume regulation and the kidney were omitted from consideration.

Protracted ingestion of water and the continual formation of hypotonic urine may lead to a functional concentrating defect simulating diabetes insipidus in normal persons and may occur as the result of psychogenic polydipsia in certain abnormal states.[45] Dietary intake appears to be an important determinant modifying the excretion of osmotically nonobligated water, i.e., free-water clearance. Kleeman and associates[46] have clearly demonstrated that the free-water clearance (the elaboration of a larger volume of more dilute urine) may be increased by a greater solute intake.

Extraction of sodium from tubular fluid plus ADH-dependent impermeability to water of distal tubule epithelium is the major determinant of a dilute urine; however, inability to elaborate a concentrated urine also may result from potassium deficiency per se in

experimental animals.[91] A diabetes insipidus-like picture of polyuria, polydipsia and impaired concentrating power occurs in rats and dogs shortly after they are placed on potassium-deficient diets.[14, 43, 91] In man, also, severe potassium depletion is associated with inability to elaborate a concentrated urine. Vasopressin does not alter the isosthenuria, the tubular membranes apparently being unresponsive to this hormone. This potassium depletion syndrome has been observed in numerous clinical situations, among them chronic diarrhea,[73] primary

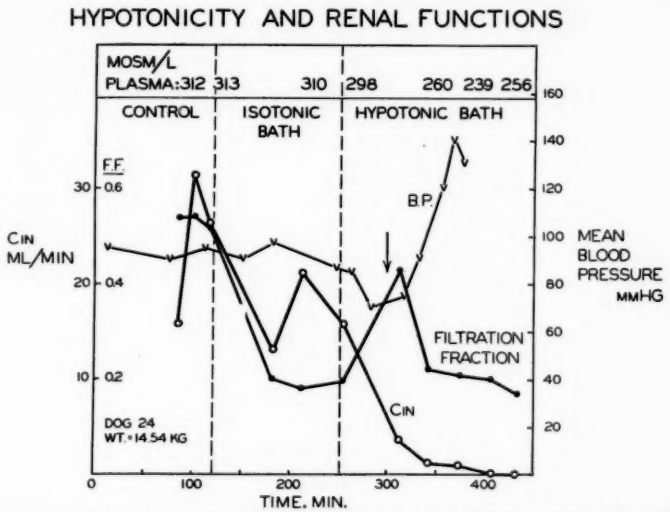


Fig. 14. Induction of hypotonicity in dogs by vivo-dialysis induces a fall in glomerular filtration rate largely at the expense of renal blood flow despite elevation of systemic blood pressure after injection of a pressor agent, Aramine, at 297 minutes.

aldosteronism,[16] cystinosis,[56] and many renal diseases. The functional defect appears to be reversible, since in chronic diarrhea and aldosteronism, at least, the capacity to concentrate the urine returns after replacement of body potassium stores. More complete reviews of this phenomenon are available.[74]

OSMOTIC DIURESIS

When an unreabsorbed solute of low molecular weight is introduced into the plasma and thereafter appears in the glomerular filtrate, the rate of urine flow is increased roughly in proportion to the plasma concentration attained by the solute. This phenomenon is termed "osmotic diuresis." Urea, glucose, mannitol, sucrose, other complex carbohydrates, sodium thiosulfate, sodium p-aminohippurate and hyper-

tonic sodium chloride solutions will produce osmotic diuresis. With osmotic diuresis as much as 50 per cent of the glomerular filtrate may be excreted in the urine. Wesson and Anslow[104] reason that most of the increased excretion results from decreased reabsorption of filtrate in the proximal tubular system. The distal tubule cannot sufficiently modify the composition of the excessively large quantity of proximal tubule fluid entering it. Accordingly, the excreted urine closely resembles proximal tubule fluid. Rapoport, Brodsky, West and Mackler[71] demonstrated that urine flow during osmotic diuresis has a direct exponential relationship to solute excretion in hydropenic man. At maximal rates of urine flow the osmolality of the urine decreases to approach, but never reaches, the osmolality of the plasma. Thus with osmotic diuresis the solute concentration of the urine is always greater than that of the plasma, i.e., osmolalities of more than 300 milliosmols per liter.

A water diuresis also may be characterized by increased excretion of solutes, but in this instance the concentration of solute in the urine is always less than simultaneous concentrations in the plasma, i.e., below 300 milliosmols per liter. In an osmotic diuresis, loss of the principal extracellular electrolytes sodium and chloride is approximately proportional to urine flow, while losses of intracellular electrolytes potassium and phosphate may be independent of the excretion of other solutes or urine flow.[72] On the other hand, administration of sodium salts produces an increased potassium loss, while administration of a nonreabsorpable anion, such as sulfate, decreases the chloride loss. Studies of osmotic diuresis led to the postulate of osmolar clearance, as noted above, to describe the reabsorption or excretion of osmotically nonobligated water in the distal segment at a point beyond which active reabsorption of sodium occurred.

Diabetic acidosis provides a classic clinical situation in which osmotic diuresis induces an alteration in electrolyte equilibrium. Nonmetabolized glucose serves as the osmotic diuretic and sweeps out the principal available ions in the glomerular filtrate, sodium and chloride, thus depleting extracellular fluid. Although titratable acid and ammonium excretion are increased, excretion of organic acids, reduction in buffer base, increased pCO_2 tensions, and depletion of both extracellular (bicarbonate) and intracellular (phosphate) buffers available for addition to the urine lead to inadequacy of the hydrogen ion exchanging mechanism.[68] Augmented excretion of sodium and potassium, with resultant profound depletion of body stores of these ions, then follows.[61] Thus conservation of extracellular and intracellular cations in the repair of diabetic acidosis is largely dependent upon restoration of hydrogen ion exchanging mechanisms and cessation of

osmotic diuresis achieved when metabolism of glucose is improved by the administration of insulin.

Somewhat similar reasoning may be used to explain the inadequacy of solutions such as "normal" saline* in 5 per cent dextrose to repair the dehydration attending diarrhea. Continuing losses of fluid via skin, lungs and in the dilute stool lead to concentration of the remaining solute in the body. "Normal" saline in 5 per cent dextrose has a solute concentration of approximately 600 milliosmols per liter. After the glucose has been metabolized the net concentration of solute is 294 milliosmols per liter and fails to provide water in excess of solute. As evaporative, renal and stool losses continue, the resultant hypertonicity can be corrected only by removal of solute in excess of water in the urine. The situation is analogous to that of osmotic diuresis produced in hydropenic man. Thus the resultant osmotic diuresis exaggerates urinary losses, further depletes body stores of essential electrolytes and augments dehydration.

ACIDIFICATION OF THE URINE

The original studies of neutrality regulation of the body fluids were provided by the work of Henderson.[40] An early and significant application of his thesis to clinical medicine was reported by Gamble, Ross and Tisdall in their classic study of *The Metabolism of Fixed Base during Fasting*.[27] The two major moieties of acid-base adjustment in construction of the urine were defined as a net saving of base (cation) by secretion of urine at the lowest permissible range of acidity and a regulated substitution of ammonium ions for "fixed" base to cover acid radicles as they entered the urine. The saving of base by secretion of an acid urine was further defined as the removal of acid phosphate and several organic acids titrated together and known as "titratable acidity."[41] Later Gamble[23] indicated that the mechanisms for such selective reabsorption and determination of acid-base structure of the body fluids were still invisible. Recent observations appear to have clarified these mechanisms and have supplemented, but not displaced, the conceptual edifice erected by Gamble more than 35 years ago. It is not the purpose of this paper to review all details pertaining to the renal regulation of the acid-base balance, since these are well described elsewhere.[30, 65, 68]

Acidification of the urine currently is thought to depend on exchange of hydrogen ion for sodium, reabsorption of bicarbonate and

* "Normal" in chemical terms would be 1 hydrogen equivalent, or a 1000 mEq. per liter sodium chloride solution. "Physiologic" salt solution would contain 100 mEq. of chloride per 140 mEq. of sodium. Therefore 0.85 per cent saline solution is neither "normal" nor "physiologic"; it *is* approximately isotonic (294 milliosmols per liter).

diffusion of ammonia. Pitts and associates[69, 80] demonstrated that neither bicarbonate nor dibasic phosphate reabsorption could account for the high rate of titratable acid excretion in urines of high buffer content during metabolic acidosis and confirmed Smith's[89] postulates that acidification of the urine could be explained only if hydrogen ions were added to the urine by tubule cells in excess of the quantity filtered. Pitts believed that hydrogen secretion was accomplished by an ion exchange mechanism in tubule cells after carbon dioxide had been hydrated by activity of the enzyme carbonic anhydrase. The immediate dissociation of carbonic acid liberated hydrogen ion, which exchanged mol for mol with sodium in the tubular lumen. It should be recognized that other interpretations could apply to the facts observed by Pitts. For example, Menaker indicated that reabsorption of carbonate ion from glomerular filtrate with the residual hydrogen ion remaining in the luminal fluid could account for the excess hydrogen ion present. He constructed a theoretical model to demonstrate the process in vitro.[53]

Brodsky[13] recently postulated that active reabsorption of sodium bicarbonate per se, if it occurs in an area permeable to carbon dioxide, would also be compatible with the data.[13] This hypothesis is more complicated than the delightfully simple one envisioned by Pitts, since it would involve cyclic generation and reabsorption of both bicarbonate and carbon dioxide, as well as active transport of both bicarbonate and sodium ions simultaneously. As bicarbonate was absorbed from the urine, pH would fall. Carbonic acid in the lumen would interact with nonbicarbonate buffers to yield titratable acid and more bicarbonate. Carbon dioxide from blood would have to diffuse into the luminal fluid along the existing gradient to form carbonic acid and maintain the cycle. The limiting feature in this system appears to be the rate at which carbon dioxide in the urine could be hydrated, since carbonic anhydrase is not present in the lumen.[6] The elevation of carbon dioxide tension (pCO_2) in alkaline urine to higher than plasma levels is usually taken as evidence that hydrogen ion is secreted into the urine. Bicarbonate reabsorption was shown to be proportional to plasma pCO_2.[75] It was Pitts' conception that the excess carbon dioxide in the urine resulted from dissociation of bicarbonate in the luminal fluid. The original concept did not explain the reported observation that carbon dioxide tensions below those of the plasma could occur in acid urines of low buffer content.

Kennedy, Orloff and Berliner[44] suggested that the carbon dioxide tensions observed in bladder urine resulted from admixture in the collecting ducts of urines from individual tubules with differing pH's. As Orloff[65] indicates, intracellular carbonic acid concentration rises when plasma carbon dioxide tension is elevated, since carbon dioxide

diffuses readily across the cell membrane, but this does not define the source of subsequently extruded hydrogen ion. Either elevated carbon dioxide tension or reduced cell pH would produce the same result. Nor does secretion of hydrogen ion into the tubule lumen necessarily result in acidification of the urine. For example, sodium may exchange with hydrogen and chloride with hydroxal ions; or chloride could be passively reabsorbed along a gradient of negative electrical potential created by active sodium transport and back diffusion of hydrogen. A nonreabsorbable anion (para-aminohippurate) would also compel H^+ excretion, despite inhibition of carbonic anhydrase activity.[57] In any case, no change in pH of luminal fluid or of the cells would be expected, since bicarbonate ion would not be produced, nor the hydration of carbon dioxide altered. Interference with the carbonic anhydrase system inhibits acidification of the urine by diminishing the rate at which metabolic carbon dioxide is hydrated. This appears to be the essential rate-limiting step in the process of urinary acidification.

Bicarbonate reabsorption, another factor leading to acidification of the urine, is dependent upon hydrogen ion exchange, and this, in turn, upon carbonic anhydrase activity. It is now thought that virtually all filtered bicarbonate is indirectly reabsorbed after dissociation in the lumen. The released carbon dioxide diffuses into the cell as a result of increased pCO_2 tension in the medium, and is hydrated as a result of enzyme (carbonic anhydrase) activity. Reabsorption is accomplished by transfer of the newly synthesized HCO_3 into the peritubular plasma with an accompanying cation, mostly sodium. Thus the bicarbonate returned to the plasma is a different ion than the bicarbonate appearing in the glomerular filtrate.

Weak bases diffuse from cells according to a physical chemical gradient and may serve as hydrogen ion acceptors in the tubule lumen, thus contributing to acidification of the urine. As indicated by Milne et al.,[59] ammonium excretion is dependent both on the rate of production within the tubule cells and on the rate of diffusion into the luminal fluid. Ammonium production is an enzymatic process involving at least four possible enzyme systems: glutaminase, l-amino acid oxidase, glycine oxidase, and transaminase. Concentrations of the first three enzymes have been found increased in chronic ammonium chloride acidosis after prolonged administration of a carbonic anhydrase inhibitor and possibly potassium depletion. At any given rate of production the diffusion of ammonia from cells into the tubular fluid is regulated by physical chemical laws governing the diffusion of nonionized weak bases. In essence, diffusion is inversely related to pH of the surrounding medium: the lower the pH, the greater the ammonia diffusion. The production of ammonia (NH_3) appears to be a function of systemic changes affecting intracellular enzymatic activity, but the

quantity of ammonium (NH_4^-) in the urine is dependent upon local conditions in the luminal fluid.

In a now classic paper, Berliner, Kennedy and Orloff[7] explored the paradoxical observation of an acid urine occurring during systemic metabolic alkalosis. Their studies suggested that although urinary acidification occurred by exchange of sodium for hydrogen in the tubular lumen, potassium competed with hydrogen ion for some common mechanism or pathway by which sodium was reabsorbed. Thus,

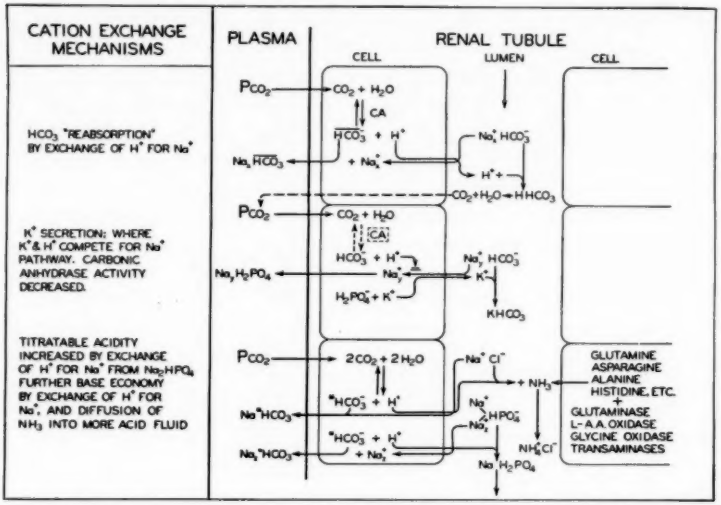


Fig. 15. Factors contributing to acidification of the urine with particular reference to cation exchange mechanisms and the elaboration of ammonia are schematically illustrated. The top section refers to the sodium-hydrogen ion exchange processes yielding bicarbonate reabsorption; the middle diagram illustrates the process of potassium secretion in which phosphate is arbitrarily chosen as the reabsorbed anion; and the bottom diagram illustrates the conservation of cation achieved by titratable acidity plus ammonium production.

in addition to elaboration of nonionized weak bases, acidification of the urine and maintenance of acid-base balance in the extracellular fluid are associated with at least two other intracellular changes, i.e., hydration of metabolic carbon dioxide with extrusion of hydrogen ion, and secretion of intracellular potassium. Secretion of potassium—i.e., when the quantity of potassium excreted in the urine is greater than the amount simultaneously filtered—provides a mechanism for reabsorption of sodium in situations in which hydrogen ion production is limited or large loads of potassium are infused.[8] In clinical states in which increased sodium reabsorption is a prominent feature, as in nephrotic edema, excretion of a nonreabsorbable anion requiring equiva-

lent amounts of cation may be used to demonstrate the exchange of sodium for potassium. Potassium then serves as the predominant cation-equivalent for the nonreabsorbable anion secretion.[58] It has been suggested that the secretion of potassium was occasioned in large part by a low filtration rate which carried limited quantities of sodium to the potassium exchanging site; hence potassium exchanged for H^+ ion, or served to cover excess anion.[48] Recent observations indicate that high rates of sodium excretion appear necessary to sustain potassium secretion in the distal tubule.[18] It appears that the observations also might be explained by persistent excretion of nonreabsorbed anion.

A schematic diagram of the principle mechanisms for urinary acidification is shown in Figure 15. Some features of various disturbances in acid-base balance relating presumed changes of intracellular hydro-

TABLE 9. *Relative Composition of Urine and Body Fluids during Various States of Acid-Base Disturbance*

STATE	URINE					EXTRACELLULAR FLUID SERUM				INTRACELLULAR FLUID MUSCLE	
	pH	Tit. Ac.	HCO_3^-	NH_3	K^+	pH	pCO_2	HCO_3^-	K^+	pH	K^+
Metabolic acidosis	−	N or +	N or −	+	N	−	N	−	+	−	N or +
Metabolic alkalosis with potassium depletion	−	+	−	+	−	+	−	+	−	−	−
Respiratory acidosis	−	+	−	+	−	−	+	+	N	−	N
Respiratory alkalosis	+	−	+	−	+	+	−	−	N	+	N or −
Effect of potassium infusion	+	−	+	−	+				+	+	N or +

Explanation of symbols: −, decreased; +, increased; N, normal.

gen and potassium concentration and urinary acidification are recorded in Table 9.

It should be noted that the kidneys, with generous assistance from the lungs, which alter carbon dioxide tension, are the major regulators of acid-base equilibrium. However, body cells also participate in this phenomenon and may provide some buffering capacity to counter excess hydrogen ion or bicarbonate ion accumulation in the absence of renal function[29, 96] and may provide an excellent source of potassium for exchange with extracellular sodium and hydrogen ions, thus serving as an extrarenal, second line of defense in regulation of acid-base balance.[17, 81]

Perhaps the most remarkable feature of renal regulation of acid-base balance is not to be found in the extremes of metabolic or respiratory disturbances. Rather, the operational consistency which regulates the pH and buffer concentrations of the body fluids with remarkable precision during growth and the vicissitudes of daily life with its varying activity, differing loads provided by ingestion of food or drink, and illness, deserves greater attention.

HORMONAL FACTORS

Evidence available at present indicates that only one hormone is essential to the primary renal regulation of body fluid composition and volume. This is the antidiuretic hormone (or substances) elaborated by the neurohypophysis. The role of the antidiuretic hormone is currently interpreted as one of direct action on the distal tubular epithelium to increase its permeability, as indicated previously. In the absence of sufficient amounts of antidiuretic substance in the circulating plasma, the distal tubular epithelium remains impermeable to water, according to current concepts. However, reabsorption of water by the renal tubules can and does occur without dependence upon this antidiuretic substance. ADH apparently exerts its maximal effect by increasing urinary concentration as a result of reducing the volume of free water. This occurs over an observable range between maximal dilution and isosthenuria. The concentrating apparatus in the final collecting ducts and surrounding hypertonic interstitial fluids are probably responsible for the elaboration of maximally concentrated urine, which approximates 1400 milliosmols per liter in man and 2000 to 3000 milliosmols per liter in the dog.

Much interest has attended evaluation of the role of the adrenal cortical steroids in the regulation of sodium reabsorption.* It has long been evident on clinical grounds that while potassium is retained, excessive sodium is lost from the body, with an osmotic equivalent of water and subsequent depletion of extracellular fluid volume, when secretion of adrenal cortical hormones is deficient or absent, as occurs in Addison's disease or after bilateral adrenalectomy. Of the adrenal cortical hormones, aldosterone appears to have the greatest relative sodium-retaining effect in the species studied.[79] However, as emphasized by Smith,[88] Selkurt[83] and by Wesson,[102] though studies of steroid excretion in the urine provide a coincident correlation with excretion or retention of sodium, they need not imply a causal relationship; nor, because of metabolic transformations, does an increased excretion of adrenal steroids in the urine imply increased elaboration by the adrenal gland. The actual effect of steroids such as cortisone, ACTH, aldosterone, hydrofluorocortisone and others on total sodium reabsorption is relatively small. When the sodium load is low, the steroid hormone activity increases the efficiency of sodium reabsorption. As indicated by Strauss,[94] adequate functioning of renal tubule epithelium may re-

* Nowhere better summarized than by Homer Smith,[90] as follows: "A pair of endocrine glands, located just above the kidneys, have long been thought to have (among other functions) something to do with the renal conservation of sodium. I have noted that in 1951, 1952 and 1953, approximately 14,598 papers were published on these glands, and we still do not know anything much about them except that they somehow promote the tubular reabsorption of some fraction of the filtered sodium and that, in their absence, as Loeb and his colleagues showed many years ago, excessive loss of sodium in the urine leads to depletion of the extracellular fluid."

quire the presence of adrenal cortical hormones, which play a facultative, permissive role, but not a regulatory one.

Thyroid hormone increases filtration rate in the dog, particularly after hypophysectomy.[37] It has been observed for years that patients with myxedema, either primary, or secondary to anterior pituitary deficiency, cannot dispose of a large water load and may conceivably have altered tubular reabsorption of sodium, although evidence on this is not clear.

Growth hormone, on the other hand, seems profoundly to affect tubular function, including sodium chloride reabsorption. In hypophysectomized dogs growth hormone restores depressed clearance to preoperative levels, and in normal dogs produces an increase in inulin clearance.[105] The details are reviewed by Wesson.[102] The available data in man suggest that growth hormone influences sodium chloride reabsorption through its effect on all renal functions which could be mediated via either thyroid or adrenal cortical stimulation. In the dog, growth hormone appears to act directly upon the kidney.[105]

VOLUME REGULATION

Many years ago Henderson[42] pointed out that regulation of volume in biologic systems provided an outstanding challenge to the investigator. In the economy of the organism, defense of concentration appears to take priority over volume.[23, 42, 67]

The mechanism by which volume of body fluids is regulated still remains a challenging mystery. The role of thirst, appetite, central nervous system, circulatory, humoral and possibly neurogenic factors with their influence upon renal function has recently been delectably described by Strauss.[94] The renal excretion of water modified by the supraoptico-hypophysial system appears to be the major determinant of body fluid content. The regulation of the volume of cell fluid appears to be controlled by the effective osmotic pressure of the extracellular fluid, and this in turn by excretion of sodium and action of diuretic hormone under normal conditions. Strauss suggests that the most important factor regulating the renal excretion of salt is the volume of extracellular fluid, more specifically, interstitial fluid. It has been suggested that the critical area where this factor becomes effective is in the cephalad portion of the body.

Most studies relating to a search for a volume receptor have recognized the importance of the circulating plasma in this regard. Procedures which affect circulation by increasing blood pressure or circulatory volume, such as saline infusion, whether isotonic or hypotonic, recumbency versus sitting or standing, compression of the legs by elastic bandages, closure of an arteriovenous fistula in the leg, and so on, tend to increase sodium excretion and thereby decrease body fluid volume. Procedures which diminish blood volume or cause pooling in the extremities tend to decrease sodium excretion and usually diminish water excretion with an increase in body fluid volume. Observations on recumbent versus sitting subjects[95] or with venous

occluding cuffs applied around the necks of seated subjects[99] suggest that if a volume-regulating center exists, it appears to be located within the skull. Peters and associates[101] described a salt-losing state with certain forms of intracranial disease; however, another group also observed excessive sodium loss and hyponatremia in association with some chronic pulmonary lesions.[82]

Teleologically, the existence of a volume receptor would nicely complement the presence of an osmoreceptor. The latter has been described by Verney[98] and is concerned with regulation of the osmolarity of the body fluids through variation in excretion of water, as departures from isotonicity occur. The volume receptor would presumably have the important function of regulating the quantity of sodium excreted with isosmotic amounts of water and thereby determine the volume of extracellular fluid. Such a relationship has been postulated and the nature, location and mode of action of the salt and water volume receptors critically reviewed as "an exercise in physiologic apologetics."[90] Volume in biology still remains a challenge!

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29th Street and Ellis Avenue
Chicago 16, Illinois

DEHYDRATION, SALT DEPLETION AND POTASSIUM LOSS

Theoretical Considerations

MALCOLM HOLLIDAY, M.D.

THOMAS J. EGAN, M.D.

The disturbances encompassed by the conditions cited in the title of this article are concerned with the loss of water or electrolyte from either extracellular or intracellular fluid. The description of body fluid divided into these two major phases has already been detailed (p. 5*ff.*). This clinic is concerned with those factors governing the distribution of water and electrolyte and the clinical effects of deficits of water and/or electrolyte incurred in disease.

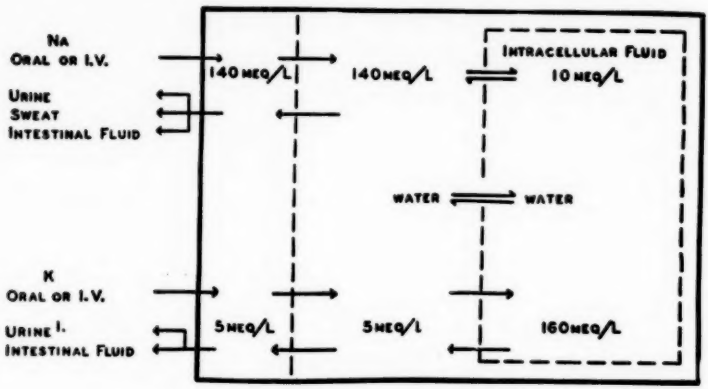
Body water comprises 60 to 75 per cent of total body weight. About two thirds of the water is intracellular and the remaining third extracellular. The principal electrolytes of extracellular fluid are sodium and chloride. For the purposes of this discussion these ions are considered to be exclusively extracellular* and further to comprise most of the solute of extracellular fluid.† The fact that sodium and chloride do not accumulate in intracellular fluid except as noted means that addition of sodium chloride or salt increases the total solute of extracellular fluid

* It is recognized that sodium exists in bone and cartilage and to a less extent in muscle and that chloride is in red cells and probably liver and brain. However, the acute changes described here are largely confined to net changes in extracellular sodium and chloride.

† In acute hyperglycemia such as develops in diabetic ketosis, blood glucose may make an important contribution to the solute of extracellular fluid. Like sodium and chloride, glucose is only slowly diffusible into cells, so that its concentration in extracellular fluid reflects that of a solute not in intracellular fluid. Accordingly, a sudden increase in glucose concentration results in an increase in extracellular solute, an expansion of volume derived from intracellular fluid and a dilution of sodium.[23]

without changing the total solute of extracellular fluid, and conversely that loss of salt diminishes the total solute of extracellular fluid with no direct loss of intracellular solute. This cycle is illustrated in Figure 16 in the case of sodium.

Potassium and its anions similarly account for most of the solute in intracellular fluid. These electrolytes are not in free equilibrium with extracellular fluid, although they gain access to cell fluid through extracellular fluid as indicated in the potassium cycle in Figure 16. The potassium cannot be lost from intracellular fluid without passing through



1. May be excreted by transport through renal tubular cells.

Fig. 16. Circuit of sodium and potassium in body fluid.

extracellular fluid. The mechanism controlling potassium distribution and excretion is considered elsewhere in this section.

Water is freely permeable between the two phases, its distribution being such that the concentration of solute in the two phases is always equal. So long as total intracellular solute is constant, any change in solute concentration will be dependent on a net change in body water without a proportional change in extracellular solute (salt) or on a net change of extracellular solute without a proportional change in water. Such changes in solute concentration are reflected by changes in serum sodium concentration. This important principle was first described by Darrow and Yannet[7] in 1935.

DEHYDRATION

Dehydration is defined as a loss of fluid without a loss of supporting tissue. Losses of body fluid associated with fasting, cachexia or glyco-

genolysis are not examples of dehydration. In practice we generally think of dehydration as a contraction of extracellular fluid volume in relation to cell mass. In this latter connotation, dehydration, i.e., contraction of extracellular fluid, can occur from an external loss of water and salt, from salt loss with no water deficit and from water loss alone. Intracellular dehydration may also occur, and its significance is considered separately.

Dehydration of extracellular fluid is either isotonic, hypotonic or hypertonic. *Isotonic dehydration* implies a proportional loss of water and salt, *hypotonic dehydration* describes a loss of salt proportionately greater than the loss of water, and *hypertonic dehydration* occurs when water loss is proportionately greater than salt loss. Primary water intoxi-

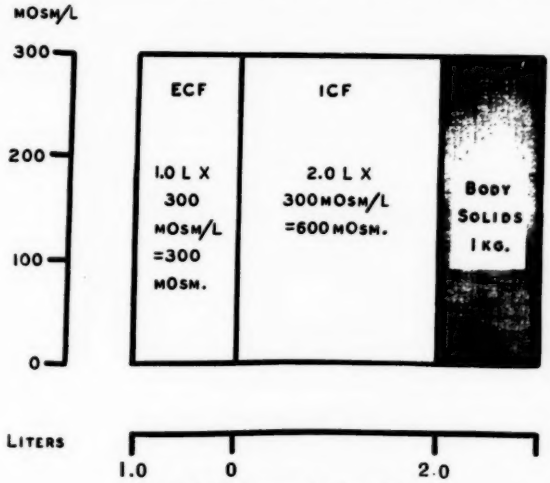


Fig. 17. Model normal 4-kg. child.

cation has certain properties in common with salt depletion, and excess sodium chloride retention has certain clinical and physiologic properties similar to hypertonic dehydration, so that changes attending these states are also described. States of hypotonicity in which neither salt depletion nor water intoxication exists are briefly mentioned to permit their differentiation from the other conditions.

The factors governing the changes in water and electrolyte distribution that occur with these conditions are illustrated by using a clinical model (Fig. 17). This model in the normal state is a 4-kg. child who has 3.0 liters of total body water consisting of 2.0 liters of intracellular fluid and 1.0 liter of extracellular fluid. The concentration of solute in each phase is 300 milliosmols per liter, so that extracellular fluid has a total of 300 milliosmols (1.0 liter $\times$ 300 milliosmols per liter) and

intracellular fluid a total of 600 milliosmols (2.0 liters × 300 milliosmols per liter). Serum sodium concentration in extracellular fluid is an index of solute concentration and can be estimated in these examples by dividing solute concentration by 2 and subtracting 10 (for example, 300 ÷ 2 — 10 = 140 mEq. per liter). The models presume known losses of water and/or salt. The changes in extracellular and intracellular volume and solute concentration are derived from this information.

Two simple equations are used in deriving this information. Solute concentration is determined by dividing total body solute by total body water without reference to either phase. This is possible since solute

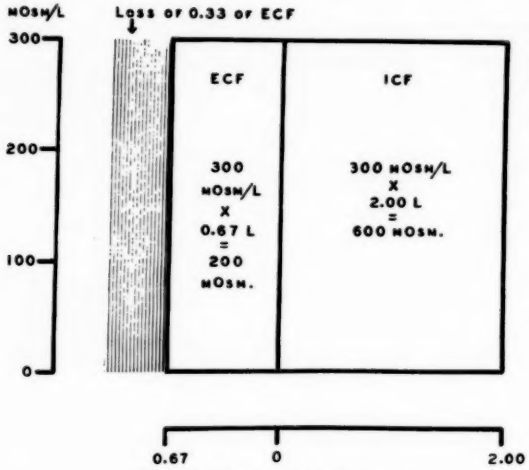


Fig. 18. Isotonic dehydration.

concentration in the two phases is equal because of the diffusibility of water. Volume in either phase is determined by dividing the total solute in that phase by solute concentration. For example, in the original model there are 900 millisomols of total solute in 3.0 liters of body water. Solute concentration in either phase is then 300 milliosmols per liter (900 milliosomols ÷ 3.0 liters). The volume of intracellular fluid is calculated in this instance by dividing total intracellular solute by solute concentration (600 milliosmols ÷ 300 milliosmols per liter) and is 2.0 liters. In the succeeding five examples in which salt and water changes are illustrated, intracellular solute remains constant (600 milliosmols).

1. Isotonic Dehydration (Proportional Loss of Salt and Water). This results in a simple reduction in extracellular volume. In this example a loss of 50 mEq. of sodium chloride, or 100 milliosmols of extracellular solute, is accompanied by loss of 0.33 liter of extracellular water (Fig. 18). Solute concentration and serum sodium

concentration remain unchanged. There is no change in intracellular volume or concentration.*

2. Hypotonic Dehydration (Hyponatremic Dehydration). Salt depletion is generally accompanied by some water depletion. To simplify the illustration, however, an example of pure salt loss will be considered. Using the same model, let us assume a loss of 75 mEq. of sodium chloride (150 milliosmols of extracellular solute), so that there remain 150 milliosmols of extracellular solute. No water loss occurs (Fig. 19, *A*). Total solute is now 750 milliosmols, and total water remains 3.0 liters. With the equilibration of water (Fig. 19, *B*) solute concentration in both phases becomes 250 milliosmols per liter (750 milliosmols ÷ 3.0 liters). Extracellular fluid volume is reduced to 0.6 liter (150 milliosmols ÷ 250 milliosmols per liter) by the diffusion of water into intracellular fluid. Intracellular fluid volume consequently increases to 2.4 liters. Serum sodium is approximately 115 mEq. per liter. Despite no loss of water, the loss of extracellular solute has occasioned a substantial reduction

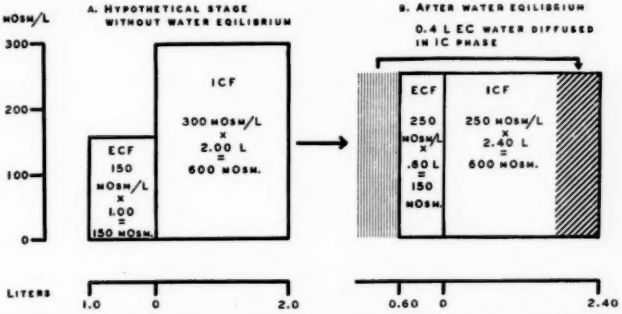


Fig. 19. Hypotonic dehydration—hyponatremia from salt depletion.

in extracellular volume and an expansion of intracellular volume with a consequent dilution of solute in both phases.

3. Water Intoxication with Resulting Hyponatremia. This example is included to illustrate the effects common to water intoxication and salt depletion on intracellular fluid and the differing effects on extracellular volume. In the model we will assume an expansion of total body water by 600 cc. or 0.6 liter (Fig. 20). The new volume of body water is 3.6 liters, and solute concentration is 250 milliosmols per liter (900 milliosmols ÷ 3.6 liters). The volume of extracellular fluid is 1.2 liters (300 milliosmols ÷ 250 milliosmols per liter) and of intracellular fluid is 2.4 liters (600 milliosmols ÷ 250 milliosmols per liter). As before, serum sodium is 115 mEq. per liter. The gain of water is proportionately distributed between the two phases according to the total solute of each, so that solute concentration of the two phases is equally reduced. As in salt depletion, intracellular fluid is expanded, and its solute concentration is decreased; however, in this instance extracellular volume also is expanded.

4. Hypertonic Dehydration (Hypernatremic Dehydration). Although some loss of salt also may occur, its loss is proportionately smaller than the loss of water. In the example an instance of pure water deficit will be described to illustrate the effects of a water loss alone. A loss of 600 cc. (0.6 liter) of water with no loss of extracellular or intracellular solute is postulated. Total body water is reduced to 2.4 liters. Total solute remains at 900 milliosmols (300 milliosmols in extracellular fluid and 600 milliosmols in intracellular fluid). Solute concentration in either phase is increased to 375 milliosmols per liter (900 milliosmols ÷ 2.4 liters). The volume of

* In this instance hematocrit will rise proportional to the loss of plasma as it reflects a loss of extracellular fluid. Hemoglobin and serum protein also increase.

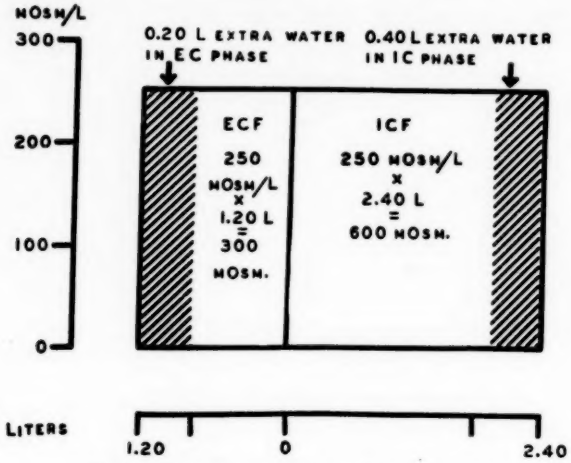


Fig. 20. Water intoxication with hyponatremia.

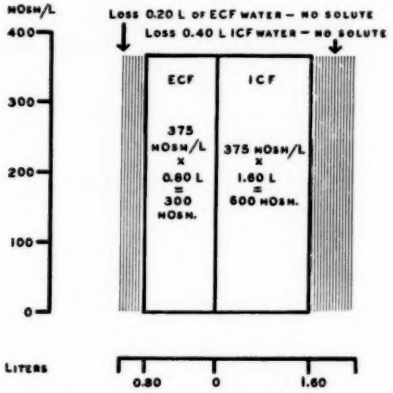


Fig. 21. Hypertonic dehydration.

extracellular fluid is 0.8 liter (300 milliosmols ÷ 375 milliosmols per liter), and the volume of intracellular fluid is 1.6 liters (Fig. 21). Serum sodium concentration is approximately 177 mEq. per liter (375 ÷ 2 — 10).

The loss of water from each phase is proportional; i.e., one third is from extracellular and two thirds from intracellular fluid, since solute was not lost from either phase.* This contrasts to the effect of isotonic dehydration (example 1) in which the total loss was from extracellular fluid.

* It is interesting to note that water loss being proportionately distributed between cells and extracellular fluid, there will be no change in hematocrit, since red cells (ICF) and plasma (ECF) are both affected. Hemoglobin and serum protein, however, will rise. In practice these parameters are of value only when used serially in following change, because the range in nondehydrated infants is too great to permit estimation of dehydration by deviations from average normal values.

5. Retention of Salt without Water. Such a state results in changes similar to those described for pure water loss except that extracellular volume is not contracted, but is expanded. The condition arises when salt intake results in salt retention without concomitant retention of water. As an example, consider the addition of 150 mEq. of salt (300 milliosmols of extracellular solute) to that already present in extracellular fluid without any gain of water. This is effect doubles extracellular solute without changing intracellular solute or total body water. Without the free diffusion of water the concentration in extracellular fluid would double (Fig. 22, A). With the diffusion of water from intracellular to extracellular fluid, concentration of solute in intracellular fluid rises, and its volume contracts. Concentration in extracellular fluid consequently rises much less than double. The total solute is 1200 milliosmols (600 milliosmols in each phase), and its concentration is 400 milliosmols per liter

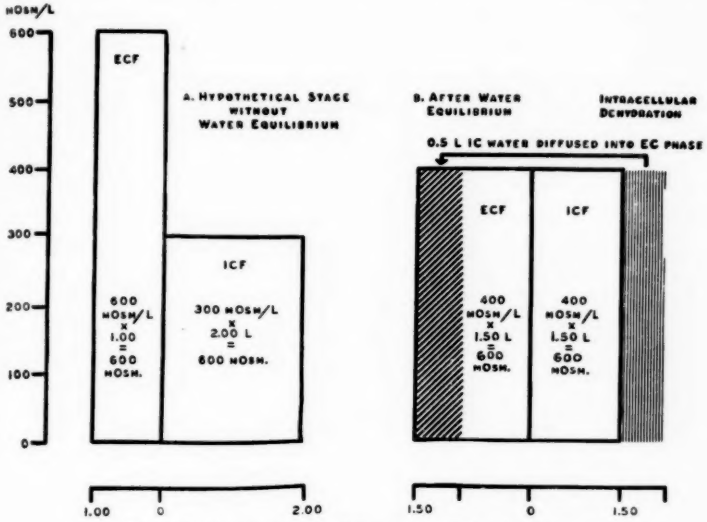


Fig. 22. Hypernatremia from excess salt retention.

(1200 milliosmols ÷ 3.0 liters). The volume in each phase is 1.5 liters (600 milliosmols ÷ 400 milliosmols per liter) (Fig. 22, *B*). Serum sodium concentration is approximately 190 mEq. per liter (400 ÷ 2 − 10).

The effects are similar to those seen in water deprivation except that extracellular volume is expanded in this instance. This is the only example of intracellular dehydration without extracellular dehydration. In actual fact, under these circumstances much of the salt and water in extracellular fluid would be excreted, so that the actual results of excessive salt administration approach those seen in water deficiency per se.

CLINICAL CONSIDERATIONS

Three changes in body fluid are described in these examples, and each can be related to some of the clinical signs and physiologic effects seen in dehydration. The change definitive of extracellular dehydration is illustrated in examples 1, 2 and 4—a *reduction in extracellular volume.* It is greatest in isotonic and hypotonic dehydration because extracellular

solute is lost in both instances. The effects of such a reduction are reflected clinically by loss of skin turgor and reduced circulatory efficiency consequent to the reduced plasma and interstitial fluid volume.

A second type of change is illustrated in examples 2 and 3—an *expanded intracellular volume* and a *decreased solute concentration*. The effect of these changes on the nervous system is described in detail elsewhere (p. 257*ff*.). The differing effects on extracellular volume noted in salt depletion (example 2) and water intoxication (example 3) account for the more frequent development of shock in the former. In addition to the central nervous system effects, both may result in varying degrees of acute renal failure. The hypertonic urine noted in some instances of water intoxication is a reflection of a greatly reduced filtration rate. These effects and the associated intracellular changes are reversible with correction of the hyponatremia. Since the renal response is common to both salt depletion and water intoxication, it is not a consequence of reduced extracellular volume, but must reflect the changes in intracellular environment. However, the reduction in extracellular volume in salt depletion increases the likelihood of renal failure.

The third principal change noted in these five examples is *contraction of intracellular volume* and an *increase in solute concentration* (examples 4 and 5). This circumstance is also dealt with in detail elsewhere and its effect on the nervous system described. The infrequency with which shock is seen in this state is due to the fact that extracellular volume is relatively less affected.

The latter two of these three changes reflect alterations in the intracellular phase and are seen in hypotonic and hypertonic dehydration of extracellular fluid respectively (examples 2 and 4). However, each may occur without extracellular dehydration (examples 3 and 5) and yet may result in similar clinical consequences.

The clinical circumstances under which the various types of extracellular dehydration are likely to develop are described in the succeeding paragraphs.

Isotonic Dehydration

The loss of salt and water with the resultant contraction of extracellular volume is the commonest and most easily remedied type of dehydration. It is most commonly seen in states of acute intestinal losses, i.e., diarrhea, vomiting, intestinal fistulas, suction, and so on, or in states of dehydration from simple fasting and thirsting in which water losses are not exaggerated. The losses in both instances are hypotonic, so that a state of hypertonic dehydration would be predicted. However, ingestion of some water and the renal excretion of extra sodium chloride tend to

compensate for the hypotonicity of the other losses, so that the net loss of water and salt is proportional.

The diagnosis of isotonic dehydration is suggested by a history of diminishing fluid or food intake in the face of diarrhea or vomiting. The physical findings are largely confined to a loss of skin turgor and, in more advanced states, signs of circulatory failure. Since most of skin water is extracellular, changes in skin turgor reflect extracellular losses. A method of semiquantitation using skin turgor as an index has been devised recently.[15] Shock in dehydration results from reduction of the plasma phase of extracellular fluid.

Loss of skin turgor and the state of shock associated with dehydration are best treated with a solution that will rapidly restore total extracellular fluid volume, i.e., normal saline or Ringer's lactate solution. The amount required clearly depends on the amount lost. To treat shock, 20 cc. per kilogram of either solution should be rapidly infused. Continued replacement of the extracellular losses will depend on the clinical assessment of the degree of loss. The limits of loss vary between 2 and 10 per cent of body weight;* providing 20 to 100 cc. per kilogram of normal saline or Ringer's lactate solution replaces this loss. The majority of instances are usually corrected with 50 to 70 cc. per kilogram. Degree of repletion is best judged by observing effects on skin turgor and circulation response. It is generally possible to achieve replacement within 24 hours of initiation of therapy. It may be accomplished more rapidly. The most extreme degrees of dehydration may not be repaired within this period. When large losses of extracellular-like fluid continue, their magnitude may not be appreciated, so that extracellular dehydration persists. This is particularly common with continued large intestinal losses. Weight change in such circumstances is helpful in evaluating the magnitude of the losses. In cases in which intestinal suction is instituted, measurement of the volume of aspirated fluid provides a direct quantitation of loss.

Loss of extracellular fluid is a clinically identifiable state; its direct replacement is feasible and should be undertaken promptly under virtually all circumstances because a diminished extracellular volume greatly impairs all physiologic function and induces undesired clinical effects. The state of anuria is not a contraindication to restoring extracellular volume to normal.[19] Extracellular dehydration can occur in edematous states. In edema, interstitial fluid is increased, but plasma volume is often reduced. Loss of both interstitial fluid and plasma can result in a loss of skin turgor and shock even though edema is still present. Assessment of

* Extracellular fluid comprises 20 per cent of body weight, so that a loss of extracellular fluid equal to 2 to 10 per cent of body weight constitutes a reduction of 10 to 50 per cent of extracellular fluid.

loss is more difficult, but replacement should be continued until skin turgor and circulation are normal even though the edema is increased.

Hypotonic Dehydration

Hypotonic dehydration occurs in those states commonly leading to isotonic dehydration in which the losses are great and are replaced by large amounts of water.

Excessive sweat loss accompanied by water ingestion similarly leads to hypotonic dehydration and a clinical state of "heat exhaustion." The classic "salt-losing states" are responsible for hypotonic dehydration when the daily salt replacement is not provided. These include the adrenogenital syndrome,[14] uretero-arachnoid shunt, pancreatic fibrosis,[9] salt-losing nephritis,*[24] cerebral salt-wasting states†[20] and chronic diarrhea, including that associated with a cecostomy or an ileostomy.

Identification of hypotonic dehydration depends primarily on eliciting a history of the factors cited above. In addition, circulatory failure and stupor develop with less change in skin turgor. Frequently the skin is cool and moist. When suspected, its presence should be established by a determination of the serum concentration of sodium and chloride, though the former will suffice.

Treatment should provide relatively more salt than water as compared to the treatment of isotonic dehydration. The repair of dehydration is often undertaken simultaneously with the provision of water required for maintenance needs (p. 29*ff*.). In isotonic dehydration this combination results in the infusion of a hypotonic solution. In hypotonic dehydration the infusion of normal saline solution until circulation and sensorium changes have improved is one method of providing extra salt. The water excreted to meet maintenance requirements makes extra salt available. Alternatively, the sodium chloride necessary to restore concentration to normal can be calculated and infused as hypertonic salt.‡ Subsequent saline and water administration can be gauged by the clinical state following the infusion of hypertonic salt.

* Salt-losing nephritis is a term which has gradually been adopted for any renal disease independent of etiology in which tubular reabsorption of sodium chloride is impaired. It is most commonly seen in association with chronic pyelonephritis.

† This condition has been described in adults. The authors know of only one pediatric case in which excess salt loss might account for hyponatremia associated with central nervous system disease.

‡ As developed in example 4, the hypotonicity affects both phases of body fluid, and the amount of salt needed must be calculated on the basis of total body water. Assuming body water to be 0.6 liter per kilogram, the milliequivalents of sodium chloride needed are equal to 0.6 × desired increase in concentration × body weight in kilograms. For example, in a 10-kg. child when serum sodium is 120 mEq. per liter and is to be raised to 135 mEq. per liter (15 mEq.), the calculation would be 0.6 liter per kilogram × 15 mEq. × 10 kg. = 90 mEq. of sodium chloride.

One form of hypotonic dehydration merits special consideration. It is that induced by subcutaneous administration of glucose solutions of low sodium content. Sodium chloride is more rapidly diffusible than glucose; hence these ions diffuse into the pool of glucose solution, leading to a loss of salt from the effective extracellular phase. Gradually, as the glucose is absorbed, the solution will be absorbed, so that the state is transient. The period of pick-up in patients already dehydrated may be as long as 12 hours, and, during the period of salt depletion, shock of serious consequences may develop. Only solutions containing 75 to 150 mEq. of salt and no more than 2.5 per cent glucose should be given in this manner. Ideally, clyses should be reserved for situations requiring supplemental sodium chloride, when it may be given as normal saline. This generally occurs in salt-wasting states when oral intake is possible, but insufficient to meet total needs.

Water Intoxication

Water intoxication may be accompanied by symptoms similar to those seen in salt depletion, although convulsions are more common with water intoxication. It is dealt with in detail elsewhere (p. 257*ff.*). In this condition correction should be effected rapidly by using hypertonic salt.

Asymptomatic Hyponatremia

Asymptomatic hyponatremia is a term reserved for those states in which serum sodium concentration is low without signs of salt depletion or dehydration and in which salt administration has no beneficial effect. It occurs in states of chronic intractable edema, for example, cardiac failure and cirrhosis of the liver. The hyponatremia associated with tuberculous meningitis and other forms of nervous system disease is another example of unexplained asymptomatic hyponatremia. When there are no circumstances which might cause salt loss and no clinical signs of salt depletion, the hyponatremia is not corrected by giving extra salt. Hyponatremia resulting from hyperglycemia has been referred to earlier. Hyponatremia accompanying lipemic states is actually an artifact, since the lipids displace serum water, and the sodium concentration per liter of serum water is normal.[21]

Hypertonic Dehydration

This includes those states in which water deficiency alone accounts for dehydration and concentration of solute (example 4) and those in which excess salt retention has occurred (example 5). The former develops in comatose patients when insufficient water is provided. It is

particularly prone to occur in patients receiving high protein tube feedings when extra water is not provided.*

The development of hypertonic dehydration in diarrheal disease has been noted with increasing frequency[26] (see p. 99*ff*.). It has been observed when infants with diarrhea have been given glucose solutions containing 50 or more mEq. per liter of sodium. These infants frequently have polydipsia and may ingest 2 or more liters of such a solution daily. After two or three days the characteristic symptoms of hypernatremia develop. The mechanism leading to this is obscure, for the fluid ingested has sufficient water in relation to salt to permit excretion of the extra salt. Presumably, when the ingested solution is hypotonic, an imbalance between those factors regulating water excretion and salt excretion develops.

Potassium Deficits and Intracellular Dehydration

In describing extracellular dehydration, loss of extracellular solute as well as water was discussed. This solute is mostly sodium chloride and can be measured. Loss of intracellular solute is less easily identified. Intracellular solute consists principally of potassium, phosphate and protein. Protein loss describes tissue catabolism and loss of cells in toto. Phosphate exists in bone and in organic complexes as well as ionic form, so that its excretion is impossible to identify as the excretion of intracellular solute. Potassium is the only intracellular solute whose loss is considered consequential in dehydration. However, its loss is not necessarily indicative of loss of intracellular solute analogous to the loss of salt from extracellular fluid. Potassium losses may reflect either tissue catabolism, glycogenolysis or the replacement of potassium in cell fluid by other cations rather than loss of intracellular solute.

Tissue Catabolism. Here 0.5 millimol of potassium is released by catabolism of 1 gm. of protein (3 millimols per gram of nitrogen). Such loss of potassium reflects only a loss of cell mass. However, when protein synthesis replaces the lost tissue, potassium is needed. If it is not available from intake, it will be derived from existing cell potassium,[18] resulting in a decrease in cell potassium concentration, i.e., potassium deficiency.

Glycogenolysis. Here 0.36 millimol of potassium is released by the catabolism of 1 gm. of glycogen.[8] As with tissue catabolism, the potassium lost reflects only a loss of glycogen as a whole. During glycogenesis, i.e., when glycogen is being replaced, potassium is needed and will be derived from cells if an intake is not provided. It is derived from extra-

* Twenty cubic centimeters of extra water are required for each gram of protein given in excess of the minimum requirement. This results from the greater urine volume necessary to excrete the products of protein catabolism.[13]

cellular fluid also, resulting in hypokalemia. This need for potassium exists during repair of dehydration when its development was associated with fasting and glycogenolysis.

REPLACEMENT OF POTASSIUM BY OTHER CATIONS. When potassium losses are not replaced, its concentration may decrease in cell fluid, and sodium,[16] hydrogen[2] or lysine[10] may replace it. This reduction in cell potassium concentration is generally what the term "potassium deficiency" implies. It develops under a variety of circumstances, including glycogenesis and protein repletion with insufficient potassium intake. In addition, it will develop when there is no potassium intake to replace normal losses. Acute chloride loss results in excess potassium excretion and potassium deficiency.

When a synthetic diet lacking in potassium and sodium is fed to rats, a minimal potassium loss results in a small but significant decrease in potassium concentration rather than a contraction of intracellular volume.[13] This experimental condition results in potassium deficit in its simplest form and illustrates the fact that such loss is not attended by a loss of intracellular water.

Sodium loading and a potassium-free intake are generally used experimentally to produce severe potassium deficiency.[16] Clinically, these conditions are reproduced in prolonged parenteral fluid therapy when no potassium is given and when saline is used in excess. Intracellular volume in relation to protein does not change, but as much as half the intracellular potassium may be lost. Much of it is replaced by sodium,[16] some by hydrogen[2] and some by lysine,[10] so that no loss of intracellular solute need be postulated.

Administration or secretion of the salt-active adrenal steroids in excessive amounts accelerates the development of potassium deficiency induced by sodium loading.[28] The deficiency may develop even though potassium is provided in amounts ordinarily sufficient to prevent deficiency. However, removing sodium from the diet virtually abolishes this effect of adrenal steroids.[22]

Metabolic alkalosis is frequently associated with the development of potassium deficiency in the circumstances just described.[8] In addition, the induction of acute alkalosis by removing chloride leads to potassium deficiency[4] and to the excretion of potassium in urine.[12] Again intracellular volume appears to be minimally affected. Metabolic alkalosis seen clinically in consequence of vomiting as in other states of primary potassium loss can be assumed to indicate potassium deficiency.

These various factors have been described to illustrate the conditions under which the principal identifiable solute of intracellular fluid can be lost. In none of these does intracellular dehydration of measurable degree develop, and all available evidence indicates that total solute concentration in cells is also maintained despite potassium losses. This is possible since other cations replace the potassium that is lost.

Potassium losses also occur in association with *metabolic acidosis* and with dehydration. Metabolic acidosis is accompanied by a great increase in anion and therefore cation excretion in urine. Potassium is among the cations excreted in greater amounts. However, neither reduction in cell concentration of potassium nor reduction in intracellular volume in relation to muscle protein has been observed.[3] Muscle catabolism and reduced total muscle mass may account for the losses. Potassium deficits have been described in diarrheal disease with acidosis[11] and in chronic renal acidosis.[25]

Intracellular dehydration with hypertonicity of the type described in example 5 results in excessive potassium excretion in experimental animals.[17] Patients with diarrheal dehydration studied by the balance technique retain water in excess of that required for extracellular expansion and retain potassium in excess of that used for glycogenesis. The implication of these findings is that intracellular water and solute are lost. The nature and sequence of such losses are not apparent, so that this interpretation is still questionable.

These various aspects of potassium loss and intracellular water loss have been developed with two purposes in mind: (1) to indicate the conditions under which potassium deficits can be predicted and (2) to form a basis for using potassium in parenteral fluid therapy.

The clinical counterparts of the experimental potassium losses are apparent in the conditions resulting in *dehydration*. Potassium losses associated with dehydration are greatest in diabetic ketosis, in chronic diarrhea, in intestinal losses in surgery, and in acute metabolic alkalosis induced by vomiting. Potassium deficiency in acute diarrheal dehydration of one or two days' duration is seldom clinically evident. Prolonged periods of potassium-free intake, especially those accompanied by high sodium intake, obviously increase the opportunity for the development of potassium deficiency.

The magnitude of potassium loss in dehydration cannot be defined in individual cases. It can at best be regarded as minimal, moderate or extensive. The range of loss observed in clinical studies may be as high as 15 mEq. per kilogram,[25] or one-third body potassium. Average losses are in the neighborhood of 4 to 8 mEq. per kilogram. However, certain factors other than loss condition the rate of replacement. Unlike losses of sodium chloride, losses of potassium cannot be replaced directly (Fig. 17). Potassium is infused into extracellular fluid. Its subsequent uptake is dependent on rate of glycogenesis, tissue synthesis, sodium-potassium exchange into the cell and possibly expansion of intracellular volume. The portion not taken up by one of these processes is either excreted or remains in extracellular fluid. Potassium can be rapidly excreted under certain circumstances, but it appears to be dependent on some adaptive mechanism so that acute loads are not always ex-

creted at a sufficient rate to avoid retention in extracellular fluid and hyperkalemia.[1] The necessity of avoiding hyperkalemia is well known. A maximum safe rate of infusion is 6 mEq. per 100 calories per day (i.e., 150 mEq. per day for the adult) in cases of severe deficiency. When little or no deficiency exists, 1 to 2 mEq. per 100 calories per day will replace the ordinary losses. A range of use is thereby established.

The contraindications for giving any potassium are particularly important in dehydration. The only circumstances in which potassium should not be given are adrenal insufficiency and renal failure. However, in acute dehydration, adrenal insufficiency may be the unrecognized cause for the dehydration, and this possibility must be excluded before potassium is given. More commonly dehydration may lead to transient renal failure secondary to shock, and this plus metabolic acidosis may result in hyperkalemia regardless of the degree of cellular potassium deficit. The latter development is particularly common in diabetic acidosis and dehydration, less so in diarrheal dehydration. When dehydration is associated with shock and renal insufficiency, potassium should not be given until circulation is restored and urine flow established. The urgency of its use varies with the degree of deficiency and the rate of cellular uptake. Diabetic patients may require potassium within a few hours of initiating treatment; infants with diarrheal dehydration seldom have clinical signs of potassium deficiency during the first 24 hours of treatment.

The decision to use potassium, when, and in what amounts in treating acute dehydration is, then, dependent on many factors. Generalizing, its use in the first 6 to 12 hours of therapy in acute dehydration is seldom indicated. When parenteral fluid therapy must be continued for more than 24 hours and no contraindication to its use exists, there is general agreement that it should be used. The rate of administration varies between 1 and 6 mEq. per 100 calories per day, depending on the need. Its use in this manner prevents hypokalemia, avoids increasing a cellular deficiency and permits initiation of replacement. Much of the replacement in severe deficiency is completed when normal dietary intake is established.

The evidence concerning a cellular deficit of water has been discussed. Ability to assess such a deficit in any individual case is doubtful. Providing for a possible deficit in the absence of hypertonic dehydration may be best related to potassium need, and water may be administered with potassium. More simply, water administered for other purposes may be increased within a safe limit of that requirement so that extra water is available to replace any such deficit. This may be accomplished by increasing the rate of water administration in acute dehydration by 50 cc. per 100 calories during the first 24 hours of therapy. Subsequent water administration is best dictated by clinical

signs of water deficit or excess. This figure is equivalent to a 50 per cent increase in the maintenance allowance for water, by whatever means it is calculated. Fortunately, the allowance for normal water needs using any rational system of calculation provides enough excess so that some may be utilized to repair intracellular deficits.

SUMMARY

Dehydration is defined as a loss of extracellular fluid, frequently associated with a loss of intracellular fluid. The dehydration may be described as isotonic, in which loss of water and extracellular solute (salt) is proportional; hypotonic, in which the loss of salt exceeds the loss of water; and hypertonic, in which the loss of water is predominant. The first two are associated with significant loss of extracellular volume, and their consequences are largely related to this change. Repair is best achieved by replacing the loss with a fluid simulating extracellular fluid, i.e., isotonic saline or Ringer's lactate solution. In hypotonic dehydration there is an associated dilution of solute and expansion of intracellular volume. These changes are associated with nervous system derangement. The loss of water leading to hypertonic dehydration with concentration of solute in both phases may lead to serious brain disorder.

The principal intracellular solute whose loss is identified in dehydration is potassium. The conditions leading to potassium losses are described. Replacement during parenteral fluid therapy for dehydration is limited by the fact that it must be given into extracellular fluid and it is subsequently distributed according to metabolic activity. For this and other reasons its administration should be calculated in terms of caloric expenditure. Between 2 and 6 mEq. per 100 calories per day, depending on degree of deficit, was suggested. The administration of water designated to repair possible deficits of intracellular water was also related to energy metabolism. Approximately 50 cc. per 100 calories per day were suggested for this purpose. The danger of giving potassium in any state in which renal failure, transient or permanent, or adrenal insufficiency exists was emphasized. This includes the period of renal insufficiency resulting from shock and dehydration.

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125 DeSoto Street
Pittsburgh 13, Pennsylvania

FLUID THERAPY OF DIARRHEA AND VOMITING

SAUL W. BRUSILOW, M.D.

ROBERT E. COOKE, M.D.

Complete fluid therapy of any dehydrated patient involves three principles: replacing those quantities of water and electrolyte lost, keeping up with continuing unusual losses, as well as keeping up with usual losses from the lungs, skin, urine and normal stool. These are termed, for convenience, deficit therapy, concomitant replacement of abnormal losses, and maintenance therapy.

Deficit therapy is the normalization of body fluids (water) and the concentration of solutes (usually electrolytes) in them. Deficit therapy of diarrhea or vomiting usually concerns itself with the losses of water and electrolyte which the patient sustained prior to medical care and thus is the initial problem facing the physician. The first phase of deficit therapy is frequently a medical emergency, since large acute losses of body water invariably lead to oligemic shock.

Concomitant replacement of abnormal losses concerns itself with replacement of those *abnormal* losses which occur while the patient is under medical care. Such losses are the result of continued vomiting and diarrhea and should be replaced by infusion of the appropriate solution, 1 ml. replaced per milliter lost.

Maintenance therapy is somewhat akin to concomitant replacement of abnormal losses, but confines itself to the replacement of those losses which occur via *normal* metabolic pathways. These include only renal, evaporative (skin and lungs) and normal stool losses.

Such a description of fluid therapy is admittedly arbitrary. It does, however, form a framework around which a plan of therapy can be

From the Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Maryland.

made for the individual patient. Since the problems of diarrhea and vomiting are chiefly those of deficit and current abnormal loss therapy, this discussion will be confined to those topics. The principles and details of maintenance therapy are discussed elsewhere in this volume (p. 29*ff.*).

GENERAL CONSIDERATIONS

The question that arises in the treatment of any dehydrated patient is, "How much water and how much electrolyte should be administered?" There can never be an exact answer to this question for the particular patient about to be treated, nor is there any laboratory test that can be done easily and quickly enough to provide an answer to this question in a clinical situation. The answer is best obtained from a combination

TABLE 10. *Probable Deficits of Water and Electrolyte in Infants with Moderately Severe Dehydration*

CONDITION	H_2O ml.	Na mEq.	K* mEq.	Cl mEq.
	Per Kg. Body Weight			
Diarrhea:				
Isotonic	100–120	8–10	8–10	8–10
Hypertonic	100–120	2–4	0–4	−2 to −6†
Hypotonic	100–120	10–12	8–10	10–12
Pyloric stenosis	100–120	8–10	10–12	10–12

* K deficits must be replaced over a period of days (see text).

† Patients with hypertonic dehydration present with an excess rather than a deficit in chloride.

of the physician's appraisal of the patient coupled with data obtained on similar patients who underwent balance studies.[2, 3, 5, 10] The actual quantities of water and electrolytes which may be lost in various conditions of moderate severity (Table 10) have been obtained by a variety of techniques such as recovery balance studies, isotope dilution methods, tissue and whole body analyses, and animal experiments. Although these studies represent only an order of magnitude of losses, they do serve as a semi-quantitative guide rather than as a precise determinant of therapy. It can be seen from Table 11 that there is a virtual identity among water losses no matter what the precipitating cause is. The electrolyte losses vary, depending on the clinical condition. What the physician actually does is to match the particular patient's state of hydration (as determined by the historical, physical and laboratory data) against a group of patients with the same clinical condition on

whom balance studies were done. One can then apply the experimental data to the patient in returning him to a normal state of hydration.

Virtually all the fluid therapy charts, the somewhat confusing formulas and the various calculating devices which provide seemingly magic information as to what fluids to administer are derived from data obtained in experimental studies of a similar kind.

Since the clinical evaluation of the patient is of the utmost importance, an accurate *history* must be obtained. Too often the severity of an infant's illness is used as an excuse to forego even the briefest history. Although it would be folly to delay emergency treatment in order to take a history, it is an extremely unusual circumstance when one of the physicians attending the patient cannot spend a few minutes to obtain some essential historical data as listed in Table 11. Of particular

TABLE 11. *Historical Data Required in Planning Deficit Therapy*

Intake	Quantity
	Kind: water, electrolyte, protein, drugs
Output	Quantity
	Kind: urine, vomiting, diarrhea, sweat, drainage
Balance	Weight change
General medical	Age
	Cardiovascular, respiratory, renal or central nervous system disease

importance are weight changes, if they are known. Frequently in our Clinic an infant is seen in an early stage of vomiting or diarrhea. At this time an accurate weight is taken, before the patient is discharged on appropriate therapy. Should the child return unimproved or in a worse clinical condition, a comparison of weights will provide an accurate gauge of the extent of dehydration, since losses in excess of 1 per cent of the body weight per day represent loss of body water. Likewise, historical data on drugs and previous therapy can be helpful. Occasionally parents use overlarge doses of salicylates or prepare home-made electrolyte mixtures which may be hypertonic. The extent of urine output may also be helpful. Usual output of urine in association with clinical signs of dehydration in the absence of glycosuria suggests a loss in the capacity of the kidney to conserve water. Contrarily, no output of urine for an extended time is an ominous sign suggesting renal tubular necrosis on the basis of shock.

The *physical signs* of disturbances in body composition are of even greater value than the historical data (Table 12). Some of the signs listed are not specific for dehydration, but are characteristic of shock, which frequently accompanies dehydration. Several further notes of caution should be made in using some of the signs listed to make a diagnosis, since these signs are extremely subjective. The clinical differ-

TABLE 12. *Physical Signs of Dehydration*

	ISO-OSMOLARITY (DEFICIT OF WATER AND SALT) ISOTONIC DEHYDRATION	HYPEROSMOLARITY (DEFICIT OF MORE WATER THAN SALT) HYPERTONIC DEHYDRATION	HYPO-OSMOLARITY (DEFICIT OF MORE SALT THAN WATER) HYPOTONIC DEHYDRATION
Skin			
Color*	Gray	Gray	Gray
Temperature	Cold	Cold or hot	Cold
Turgor	Poor	Fair	Very poor
Feel	Dry	Thickened	Clammy
Mucous membranes	Dry	Parched	Clammy
Eyeball	Sunken and soft	Sunken	Sunken and soft
Fontanel	Sunken	Sunken	Sunken
Psyche	Lethargic	Hyperirritable	Coma
Pulse*	Rapid	Moderately rapid	Rapid
Blood pressure*	Low	Moderately low	Very low

* Signs of shock rather than of dehydration per se.

entiation between isotonic, hypertonic and hypotonic dehydration is by no means as clear as the tables might indicate. Like the data of the aforementioned balance studies, these signs provide a guide rather than rigid criteria. One may find in the older child that skin turgor may be fairly normal in any type of dehydration. Perhaps the outstanding signs in such children are sunken eyeballs and dry mucous membranes.

The physical findings which characterize variations in the concentration of specific substances in the blood (Table 13) require some explanation. The characteristic signs of acidosis are increased depth and rate of respiration, which, however, may be depressed in the presence of severe circulatory insufficiency. The compensatory diminution in

TABLE 13. *Physical Signs of Variations in Concentration of Specific Ions*

Acidosis	Respiration: increased depth and rate
Alkalosis	Respiration: decreased depth and rate
Hypopotassemia	Heart: fast or slow; poor quality
	Skeletal muscle: weakness or paralyses; diminished reflexes

TABLE 14. *Laboratory Data Useful in Planning Therapy*

Serum or plasma	CO_2 content and chloride concentration
	Sodium and potassium concentration
	Protein concentration
	Serum osmolarity
Whole blood	pH
	Hematocrit
	Nonprotein nitrogen
Urine	Volume and specific gravity
	Albumin, sugar, acetone
	Sediment
Electrocardiogram	

breathing that is associated with alkalosis is usually absent in adults, but frequently striking in infants with pyloric stenosis. There may be deficits in body potassium without the physical findings listed in the table.

The *laboratory*[1] (Table 14) is helpful in planning therapy, but is not so essential that adequate therapy cannot be initiated without it. In infants with diarrhea probably a single laboratory determination is necessary to plan deficit therapy. This can be a serum sodium analysis or serum osmolarity. It has already been stated that the appraisal of deficits is a clinical one. The chief function of the laboratory will be to establish the tonicity of the dehydration caused by diarrhea. This is not to say that other determinations are not helpful. An elevated serum protein concentration or hematocrit value in a previously well nourished nonanemic patient may aid in evaluating deficits. The pres-

ence of a low or normal hematocrit value in a greatly dehydrated patient means that a significant degree of anemia must be present which should be corrected. The blood urea nitrogen or its equivalent (serum urea nitrogen or nonprotein nitrogen) may be of extreme importance in studying a dehydrated patient. In moderate to severe dehydration the nonprotein nitrogen is usually elevated in the initial stages and gradually falls to normal with rehydration. Failure to return to normal in a patient who apparently is receiving adequate therapy should suggest the possibility of intrinsic renal disease. This may have antedated the diarrhea or may have been caused by prolonged oligemic shock producing renal tubular necrosis, or occasionally in chronic diarrhea may be due to prolonged potassium deficiency. Usually in cases of diarrhea or vomiting the blood pH is not a necessary determination. In diarrhea the low carbon dioxide content is invariably of metabolic rather than respiratory origin and thus clearly represents acidosis. Similarly, in the infant with pyloric stenosis the elevated carbon dioxide content represents alkalosis of metabolic origin. However, there appears to be an increasing number of children with chronic lung disease (usually on the basis of cystic fibrosis of the pancreas or congenital heart disease with large left-to-right shunts) who are occasionally admitted to the hospital with a history of vomiting. In such cases one cannot be sure that an elevated carbon dioxide content and low chloride are not the result of diminished alveolar ventilation due to chronic pulmonary disease and thus represent a respiratory acidosis rather than a metabolic alkalosis. A blood pH can then be of great value.

DIARRHEA

Table 10 describes the order of magnitude of the deficits found in moderately severe dehydration of various types. These figures are generally agreed upon by most authors who write on this subject. There is, however, some disagreement on the best method for administration of these needed electrolytes and water. The method to be presented here offers, we feel, a consistant approach to the therapy not only of diarrhea, but also of virtually any other disturbance in body hydration. Tables 15, 16 and 17 show in outline form how an infant with moderately severe dehydration (120 ml. of fluid lost per kilogram of body weight) would be treated. Losses of about 160 ml. of fluid per kilogram of body weight represent maximum dehydration because *acute* losses in excess of this result in complete circulatory collapse and death. The clinical signs of dehydration usually are not present when less than 60 ml. of fluid is lost per kilogram of body weight. It is only with experience that the clinician can make educated guesses as to the degree of dehydration. The figures given in the tables can be modified upwards or downwards, depending on the clinical situation.

TABLE 15. *Deficit Therapy of Moderately Severe Isotonic Dehydration Due to Diarrhea in Infants*

SOLUTION	WATER Ml./Kg.	TIME IN HOURS FROM ONSET OF THERAPY	SITE	ELECTROLYTE (mEq./Kg.) IN SOLUTION GIVEN Na	K	Cl	PURPOSE
Ringer's lactate	20	0–1	IV	2.6		2.2	Expand blood volume and correct shock
Whole blood	10	1–2	IV	Not considered in deficit			Further correct shock if necessary
5 or 10% glucose or invert sugar in water	40	2–8	IV	0	0	0	Correct ketosis and H_2O,
Darrow's K lactate	60	2–8	IV or SC	7.3	2.1	6.3	K and Cl deficits
Total deficit replaced (see Table 10)	120			9.9	2.1	8.5	

These balance figures are for infants only. To convert these figures for use in older children, one must remember that the *clinical* signs of dehydration depend on percentage losses. A smaller deficit per kilogram of body weight in the older child or adult will produce similar percentage losses as greater deficits per kilogram of body weight in the young infant, since the infant's body contains relatively more water. Because of this, the moderately severely dehydrated older child will have deficits of the order of magnitude of about 75 per cent of these deficits noted in Table 10 for similarly affected infants.

After the deficit estimate has been made and therapy has been started *a position of flexibility must be taken.* Occasionally the patient may improve more rapidly than expected, and failure to revise one's initial estimates downward will result in edema and, occasionally, cardiac failure. Should the patient not be improving as rapidly as expected and signs of dehydration persist, an upward revision of initial estimates must be made.

As indicated in Tables 15, 16 and 17, therapy of acute diarrhea is invariably started with 20 ml. per kilogram of Ringer's lactate solution given rapidly. This is based on the premise that shock or borderline shock exists in acute diarrhea; thus extracellular volume expansion is the most urgent need in order to improve circulation. Administration of an approximately isotonic fluid, such as Ringer's lactate solution, for a short time expands extracellular volume effectively and has this added advantage. Because the sodium concentration of Ringer's lactate is 130 mEq. per liter, it will tend to normalize virtually any abnormal serum sodium concentration and not seriously affect normal values. Thus it represents appropriate early therapy from this standpoint when the tonicity of the diarrhea is not known with certainty. In addition, this solution is the first step in repairing deficits. It will provide about 2.5 mEq. per kilogram of sodium and about 2 mEq. per kilogram of chloride. (The other ions in Ringer's lactate are in such low concentration that they can be disregarded as far as repairing deficits is concerned, except for some improvement in bicarbonate concentration.) Referring again to Tables 15, 16 and 17, we can see that the remainder of therapy will depend on the tonicity of the diarrhea, since the remaining deficit of electrolyte is different, especially in cases of hypertonic diarrhea. It is our practice to have the essential laboratory determinations performed while the initial expansion of extracellular fluid is taking place.

Before the detailed therapy of isotonic, hypotonic and hypertonic dehydration is examined, a brief discussion of their physiologic genesis in diarrhea is in order. Although the composition of diarrheal fluid may vary somewhat, the factors determining extracellular tonicity in children with diarrhea are quantity and type of oral intake, ability of the kidney to concentrate, and skin losses.[4] In diarrhea in older children

TABLE 16. *Deficit Therapy of Moderately Severe Hypotonic Dehydration Due to Diarrhea in Infants*

SOLUTION	WATER Ml./Kg.	TIME IN HOURS FROM ONSET OF THERAPY	SITE	ELECTROLYTE (mEq./Kg.) IN SOLUTION GIVEN			PURPOSE
				Na	K	Cl	
Ringer's lactate	20	0–1	IV	2.6		2.2	Expand blood volume and correct shock
Whole blood	10	1–2	IV	Not considered in deficit			Further correct shock if necessary
5 or 10% glucose or invert sugar in Ringer's lactate	40	2–8	IV	5.2	0	4.4	Correct ketosis and H_2O, Na, K and Cl
Darrow's K lactate	60	2–8	IV or SC	7.3	2.1	6.3	
Total deficits replaced (see Table 10)	120			15.1	2.1	12.9	

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TABLE 17. *Deficit Therapy of Moderately Severe Hypertonic Dehydration Due to Diarrhea in Infants*

SOLUTION	WATER Ml./Kg.	TIME IN HOURS FROM ONSET OF THERAPY	SITE	ELECTROLYTE (mEq./Kg.) IN SOLUTION GIVEN Na	K	Cl	PURPOSE
Ringer's lactate	20	0–1	IV	2.6		2.2	Expand blood volume and correct shock
Whole blood	10	1–2	IV	Not considered in deficit			Further correct shock if necessary
5 or 10% glucose or in water	60	2–12	IV	0	0	0	Correct ketosis and H_2O, Na and K deficits
M/6 Na lactate	20	2–12	IV	3.3	0	0	
K acetate concentration*	0.5	2–12	IV	0	2.0	0	
Total deficits replaced (see Table 10)	100			5.9	2.0	2.2†	

* K acetate (Cutter) contains 4 mEq./ml.

† Even though there is no chloride deficit, it is necessary to administer this small amount in the initial solution.

(especially bacillary dysentery, in which stool electrolyte losses tend to be greater) hypotonicity may result because the child voluntarily drinks copious quantities of electrolyte-free fluids such as water and ginger ale. Infants, on the other hand, frequently suffer from hypertonic dehydration, caused by any combination of the three above-mentioned factors. The infant's inability to produce a concentrated urine (which results in a relative retention of electrolyte) constantly tends to make him hypertonic. This tendency becomes a serious factor when he is fed high solute milk mixtures[4] (such as skim milk, whole cow's milk or reconstituted evaporated milk) or home-made electrolyte mixtures which are not hypotonic enough. Should the infant reside in a very warm climate, water losses via sweat (which normally contains little electrolyte) make hypertonicity even more of a problem. By carefully considering these factors, one can attain some degree of accuracy in prediction of tonicity by history alone.

Isotonic Dehydration

When the Ringer's lactate infusion is complete, blood is occasionally given if no noticeable improvement in circulatory hemodynamics is noted. The remainder of the deficits in water and electrolyte is provided by 5 or 10 per cent glucose in water and Darrow's K lactate solution over a six- to eight-hour period. As can be seen in Table 15, 40 ml. per kilogram of the former and 60 ml. per kilogram of the latter when added to the previously given solution will approximately provide the necessary water and electrolyte. Certain precautions must be noted in using solutions such as Darrow's K lactate, which have relatively high concentrations of potassium. If these precautions are observed, there is no danger in the use of such fluids by the intravenous or subcutaneous route.[6] Because oliguria and anuria represent virtually complete contraindication to the use of potassium, there must be evidence of recent urine formation. Secondly, the aforementioned initial expansion of extracellular volume must be completed with evidence of improvement of the shocklike state. Thirdly, except under unusual circumstances no more than 3 to 4 mEq. of potassium per kilogram of body weight per day should be administered. Because of this, deficits in potassium should be replaced over a period of several days except in unusual circumstances.

Hypotonic Dehydration

In hypotonic dehydration (10 per cent of all cases of diarrhea) the deficits in sodium and chloride are greater; therefore large amounts of these ions are administered after administration of the Ringer's lactate.

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This is done as indicated in Table 16 by substituting some isotonic solution containing 5 per cent glucose instead of the 5 per cent glucose in water alone. The Darrow's K lactate is also given to provide the remainder of the water and electrolyte deficit after extracellular volume has been expanded with some isotonic fluid. The low serum sodium concentrations present do not ordinarily require abrupt elevation with hypertonic salt solutions unless there are some symptomatic manifestations of water intoxication such as convulsions.

Hypertonic Dehydration

Since the entire problem of hyperosmolarity is covered in another area of this symposium (p. 257*ff.*), our views will be only briefly presented. The therapy for hypertonic dehydration (Table 17) represents some deviation from the usual therapy of diarrhea. The principles are essentially the same, however: namely, rapid expansion with Ringer's lactate to improve circulation followed by slow replacement of the remaining deficit of water and electrolyte. Because balance studies show that the deficits of sodium and potassium are not as great and that there is no chloride deficit, but rather a chloride excess, treatment of this condition requires the use of different fluids. Furthermore, because it has been our experience that the usual rapid correction of hypertonicity seems to lead to seizures, cardiac failure and generally poor response, the fluids are administered over a 12-hour period rather than the usual 6 to 8 hours.

Other Factors in the Therapy of Diarrhea

Occasionally, while the deficit therapy is taking place, the patient will continue to pass voluminous watery stools despite no oral intake. In such cases it is essential that an estimate of losses be made, with replacement with an equal volume of a similar solution. Such losses are usually not more than 10 to 25 ml. per kilogram per day. Our practice is to use a solution containing equal quantities of Darrow's K lactate and 5 per cent glucose. This is not usually a problem because, with complete withdrawal of oral feedings, the volume of the stools decreases rapidly. Rarely do large losses occur for a prolonged period after appropriate intravenous therapy has been begun; but if they do, it may be necessary to collect all stools and measure the actual losses. Swenson[9] has commented that such losses may not be quite so obvious in children with megacolon. He has had the experience of finding large quantities of diarrheal fluid in the dilated bowel. In such cases the severity of the diarrhea may not be apparent until signs of severe dehydration occur. Drugs which inhibit peristaltic activity or methylcellulose derivatives, which absorb intestinal contents and produce a more bulky stool,

have relatively little effect on the abnormal losses in infantile diarrhea.

Although net absorption of carbohydrate, fats and proteins may be increased by feeding large amounts of milk during diarrhea, there is an unquestionable increase in the volume of stool[5] which makes the replacement of water and electrolytes exceedingly complicated and extends the need for parenteral fluids over several days.

After there has been a reduction in stool output, and the patient is rehydrated, oral feedings may commence. It is our practice to start small frequent feedings of carbohydrate and electrolyte such as Lytren, which is commercially available, or a suitable substitute which we have introduced at the Harriet Lane Home:

AMOUNT IN 1 QUART	FINAL CONCENTRATION
Sucrose ..... 50.0 gm.	5 gm. %
NaCl..... 1.7 gm.	30 mEq./L.
$KHCO_3$ ..... 2.0 gm.	20 mEq./L.

Should this be well tolerated, larger volumes are offered less frequently, and calories are added each day gradually (about 20 calories per kilogram added each day) in the form of milk. Since the volume of fluid offered orally during this stage is about 140 ml. per kilogram, the mixtures are composed of varying quantities of milk with Lytren. Premature administration of a large number of calories in the form of milk may induce exacerbation of the diarrhea.[5] In the young infant with a family history of allergy the use of a hypoallergenic feeding mixture such as Nutramigen or a soy bean mixture is recommended for the recovery phase of diarrhea, since permeability of the gastrointestinal tract to whole protein is increased during this time.[7]

Therapy of Mild Diarrhea

Many infants and children with diarrhea do not require parenteral fluid therapy. The decision for the use of oral rather than intravenous fluids rests on a clinical appraisal of the patient. If there are signs of circulatory insufficiency, lethargy, vomiting or gastric distention, parenteral therapy must be given. In the absence of these findings and in the presence of only minor signs of dehydration, mixtures of sugar and electrolyte such as Lytren may be fed with the complete withdrawal of milk initially. Parenteral therapy is indicated for infants when amounts in excess of 1.5 liters per day are required to meet continued stool losses. Infants with mild diarrhea have been observed who have taken 2 to 3 liters of electrolyte mixtures orally per day with resultant increase in the volume of stools; cessation of oral intake resulted in prompt cessation of the diarrhea. Such instances are rare and do not detract from the value of oral carbohydrate and electrolyte mixtures in the prevention of severe disturbances when given early.

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VOMITING

The major fluid therapy problem concerning vomiting in pediatrics is, of course, the therapy of *hypertrophic pyloric stenosis*. Although most of the points made about dehydration due to diarrhea hold in a general way for pyloric stenosis, there are some distinctions. In the pathogenesis of the dehydration the most important difference is the rate of loss of fluids. Because in acute diarrhea the fluids are lost over a period of 24 to 48 hours, these relatively sudden losses produce a much greater degree and frequency of shock as compared to the infant who has been losing fluid in the vomitus over a period of weeks. Although the infant with pyloric stenosis may have extreme clinical signs of dehydration, he presents more often as a severely chronically ill child rather than the acutely ill patient in shock. Because the losses are those of the acid gastric contents, there is usually a profound metabolic alkalosis associated with a large deficit in intracellular potassium.

The alkalosis occasionally manifests itself clinically as tetany. Should frank clinical tetany not be apparent, a positive Chvostek sign may be elicited. A more significant indicator of tetany in the infant is the peroneal sign (gentle tapping of the peroneal nerve as it crosses over the head of the fibula produces eversion of the foot).

Low serum potassium concentrations may reflect the intracellular potassium deficiency, but the electrocardiogram may be even more useful. These patients frequently exhibit the changes of hypokalemia: depression and broadening of the T wave and a prolonged Q-T interval. It is striking to observe these return to normal after appropriate intravenous fluid therapy. The laboratory finding of an elevated carbon dioxide content quickly resolves any difficulty in the clinical distinction between pyloric stenosis and adrenal hyperplasia. Another distinction between these two conditions is the serum potassium concentration, which is low in the former and high in the latter.

Consulting Table 10,[2] we see that larger amounts of chloride are lost in relation to sodium; for this reason, as noted in Table 18, initial expansion of extracellular volume is undertaken with isotonic sodium chloride instead of Ringer's lactate. In addition, chloride is the only anion used when completing the deficit therapy with isotonic sodium chloride and potassium chloride solutions in the order of magnitude presented in the table. Correction of the hypochloremia by administration of ammonium chloride without correction of the potassium deficit leads to continued alteration in the function of renal cells as well as other cells and subsequent difficulties in correction of the alkalosis. Although most of the deficits may be replaced within 12 hours, operation should be delayed for about 48 hours to permit further correction of the potassium deficit and allow for optimal readjustment of body functions, except in very mildly ill infants with little or no signs of dehydration. Adequate fluid therapy during this period of prepara-

TABLE 18. *Deficit Therapy of Moderately Severe Dehydration Due to Hypertrophic Pyloric Stenosis*

SOLUTION	WATER Ml./Kg.	TIME IN HOURS FROM ONSET OF THERAPY	SITE	ELECTROLYTE (mEq./Kg.) IN SOLUTION GIVEN			PURPOSE
				Na	K	Cl	
Isotonic NaCl	20	0–1	IV	3.0	0	3.0	Expand blood volume and correct shock
Whole blood	10	1–2	IV	Not considered in deficit			Further correct shock if necessary
5 or 10% invert sugar* or glucose in water	40	2–8	IV	0	0	0	Correct H_2O, Na, K and Cl deficits
Isotonic NaCl*	40	2–8	IV or SC	6	0	6	
and							
Isotonic KCl*	20	2–8	IV or SC	0	3.0	3.0	
Total deficit replaced (see Table 10)	120			9	3	12	

* These solutions should be mixed and given as one.

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tion prevents deterioration, and the stomach may be decompressed by gentle suction. Should significant quantities of gastric fluid be obtained via the suction tube, it should be replaced, using a solution containing similar concentrations of electrolytes. (Commercially available gastric replacement solutions are available containing the following concentrations in milliequivalents per liter: sodium, 63; chloride, 150; and potassium, 17.)

A cautionary comment should be made about an unusual complication of pyloric stenosis. It has been well demonstrated in animals[8] that potassium deficiency leads to defective concentrating ability by the kidneys. One occasionally finds an infant with pyloric stenosis of relatively long duration with profound alkalosis and potassium deficiency who manifests this relative inability to concentrate his urine. One must then be aware that much more water must be made available to these children.

The fluid therapy of *vomiting from other causes* follows essentially the same plan as that of pyloric stenosis. If the vomitus is bile-stained, the patient may have a small bowel obstruction. Large quantities of succus entericus are then lost, and the picture of hypochloremic alkalosis will not exist because of the increased loss of sodium. Although one can apply the general principles mentioned in this article to such a case, highly individualized care must be given to these patients.

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The Johns Hopkins Hospital
Baltimore 5, Maryland

FLUID THERAPY IN DIABETIC ACIDOSIS

GEORGE M. GUEST, M.D.

CLARK D. WEST, M.D.

The outline here presented was developed as part of a manual for use of the staff of the Cincinnati Children's Hospital. The principal features of the pathologic physiology of diabetic acidosis and coma are listed first, to emphasize the sequence of the metabolic derangements that occur at different stages in the development of and recovery from acidosis. Biochemical principles upon which a rational scheme of treatment should be based are discussed briefly, to indicate the main objectives toward which corrective therapy should be directed. The guide (Table 19) for the administration of insulin, electrolytes and fluids is designed to stress the concept that timing of the different therapeutic procedures during successive stages is highly important.

METABOLIC DERANGEMENTS

The development of diabetic acidosis and coma is the result of a vicious circle of closely interrelated factors, in which mutually aggravating secondary effects are far more damaging to the body than the initial manifestations. The principal factors and consequences are (1) insulin insufficiency or ineffectiveness; (2) impaired glycogenesis and increased glycogenolysis, hyperglycemia and glycosuria; (3) increased hepatic ketogenesis, ketonemia, ketonuria; (4) metabolic acidosis; (5) increased cellular catabolism; (6) losses of electrolytes and water from

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio.

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the body by urinary excretion, and by "insensible" water loss from the lungs with Kussmaul breathing; (7) dehydration, hemoconcentration, diminished blood volume, falling blood pressure, shock; (8) tissue cellular damage in vital organs from increased catabolism, toxic by-products and acidosis; (9) coma, associated with ketonemic narcosis and cerebral anoxia with severe acidosis.[3, 4]

The development of keto-acidosis is always initiated by insulin insufficiency.* This may be an actual lack of insulin, as with the onset of diabetes in a new case, or careless omission of the usual daily dose of insulin in cases with treatment well established, or, in the latter, failure to increase the daily dosage of insulin as needed during infections or other illnesses that lead to increased insulin requirements. Also, the available insulin, either endogenous or exogenous, may be rendered less effective by various factors; e.g., hormonal antagonists, toxins or enzymes that destroy insulin, or conditions in the body fluids accompanying acidosis, which interfere indirectly with enzymatic processes through which insulin exerts its action.

Early effects of insulin insufficiency are decreased glycogenesis, increased glycogenolysis, hyperglycemia and glycosuria, and rapidly increasing losses of nitrogen. Hepatic ketogenesis increases as the glycogen store in the liver is depleted. Ketonemia increases rapidly when overproduction of ketones exceeds both the capacity of the kidneys for excretion and the rate of utilization of the ketones by muscles and other body tissues. The ensuing development of metabolic acidosis results partly from the accumulation of the so-called ketone acids, partly from losses of mineral cations excreted with the ketones and other acid metabolites in the urine. The state of acidosis itself, with low bicar-

* PREVENTION. Under any scheme of diabetic care, whether strict or liberal from the dietary point of view, ketonemic acidosis and coma should never occur if proper precautions are observed for prompt regulation of insulin dosage at times of stress. Instructions for home management should emphasize unceasingly the signs of impending trouble to which both the children and parents should be alert: namely, polyuria, increasing glycosuria, and ketonuria. Particularly at the beginning of infections (sore throat, especially), rapidly increasing ketonuria is a danger signal more important than the degree of glycosuria. Fortunately the simple reagents now commercially available (powders, tablets, indicator papers), which make frequent testing of the urine for acetone easy, offer convenient and important aids for this phase of self-management. The finding of ketonuria with glycosuria is a double indication of insulin insufficiency, calling for immediate administration of extra doses of insulin. The development of a diabetic crisis can be arrested by extra doses of insulin when ketonuria first appears much more easily than later, when rapidly developing acidosis and other concomitant factors diminish the effectiveness of insulin. When ketonuria is found with increasing glycosuria, extra doses of quick-acting insulin should be administered at once and repeated at two or three hourly intervals until the ketonuria disappears. Usually a single extra dose of insulin, about one fifth of the daily dose of slower-acting insulin customarily used by the patient, will serve to stop the development of ketosis. Parents should be taught to do this on their own initiative; and most children of 10 years and older can learn easily to carry out this part of their self-management dependably.

bonate and low pH of the plasma, further aggravates the metabolic disturbances by directly or indirectly interfering with the action of available insulin and by accelerating catabolic processes in all tissues. Increased tissue catabolism liberates intracellular constituents (nitrogenous compounds, phosphates, potassium, and so on) to be excreted in the urine and accelerates the progressive depletion of body electrolytes.

Although dehydration is initiated by glucose diuresis, its progressive development results mainly from losses of electrolytes in the urine and consequent diminished ability of the body to retain water; such dehydration is further aggravated by "insensible" water loss from the lungs, with the hyperpnea of Kussmaul breathing. With dehydration there is concomitant hemoconcentration, diminished blood volume, falling blood pressure, shock and, finally, renal failure, which adds the element of renal acidosis to aggravate the existing state of acidosis.

Coma is the most critical manifestation of the diabetic crisis. The high mortality rate among patients who become deeply comatose rises sharply with the duration of coma, regardless of differences in treatment followed in different clinics. Irreversible tissue damage in vital organs may be ascribed to factors of increased catabolism induced by acidosis, histotoxic effects of acetoacetic and beta-hydroxybutyric acids, and to effects of lowered pH of the body fluids interfering with oxygen exchange and leading to tissue anoxia, especially in the brain.

Numerous investigators have shown that high levels of ketones in the blood of patients in diabetic coma are closely correlated with the severity of acidosis as measured by the plasma pH and carbon dioxide content. The simple qualitative test for plasma ketone level described below can afford information fully as valuable as the more complicated measurement of pH and carbon dioxide content. It is important to note that ketonemia and ketonuria often are not closely correlated. Early in the development of ketosis intense ketonuria may occur without significant ketonemia, when renal function is good and acidosis mild. On the other hand, in a patient with renal impairment and circulatory collapse, severe ketonemic acidosis may exist, with coma, when ketonuria is only slight or even absent. In patients with chronic renal disease the simple qualitative test for ketones in the blood, described below, may afford the most important information needed for the differential diagnosis of keto-acidosis, precipitated by a lack of insulin, and of renal acidosis not necessarily associated with a lack of insulin. This differential diagnosis may be critical for the guidance of immediate treatment in an unconscious patient. During treatment the degree of ketonemia appears to be closely parallel to the patient's resistance to insulin; diminishing ketonemia affords a sensitive and valuable index of effective insulin action, more informative than the level of blood sugar.

Laboratory Tests

Especially when infants and children are treated, hospital laboratories should be equipped for microchemical analyses. Many of these procedures are not only more economical of blood, but also are quicker and more accurate than methods used in the past, which required relatively large amounts of blood.

Following are a few microprocedures we have found most satisfactory for routine use, from a technical standpoint: for *blood sugar*, the Nelson-Somogyi method;[8] *blood urea nitrogen*, the method of Friedman[2] modified for small samples; *serum pH*, by the glass electrode or by the colorimetric procedure of Hastings and Sendroy;[6, 9] *serum chloride*, the method of Schales and Schales[10] adapted to microquantities by adding sulfosalicylic acid to the sample; *serum carbon dioxide content* by the Natelson microgasometer; *serum sodium and potassium* by flame photometry; *microhematocrit*.

For rapid bedside tests the high speed microhematocrit centrifuge (International Equipment Co.) is a most valuable simple aid. This apparatus represents a development of the microhematocrit method described by Guest and Siler in 1934,[5] the application of which is greatly facilitated by the improved centrifuge and accessory equipment currently available.[7] Heparinized capillary glass tubes (75 by 2 mm.)* are filled with blood obtained by skin puncture (finger, toe or heel), sealed and centrifuged 4 minutes at around 12,000 revolutions a minute.

The hematocrit tubes serve a double purpose. Measurements of the volume of packed cells furnish valuable indices of hemoconcentration, with dehydration, and of the progress of rehydration during treatment. The tubes, when cut with a file just above the packed cells, yield drops of plasma adequate for testing for ketones with the nitroprusside reagents commonly used for testing urine.† The drops of plasma can be used on these reagents directly, undiluted, or diluted serially as recommended by Duncan.[1] This qualitative test is adequate to demonstrate varying degrees of ketonemia in acidotic patients and to follow the course of disappearance of ketonemia during recovery as a sensitive index of effective insulin action (see discussion above).

TREATMENT

Insulin

The amount of insulin required depends on the age of the patient, the degree of acidosis, presence of infection, injury or other factors that initiate the crisis. In new patients initial doses may be estimated as follows:

At Ages	*Initial Dose (Regular or Crystalline Insulin) for Mild to Severe Acidosis*	
0–2 years	15–30 units	or 40–60 units/sq. M. body surface
5 years	10–20 units	
10 years	30–75 units	
15 years	40–100 units	

* These tubes are available from several sources: A. S. Aloe Co., St. Louis, Missouri; A. H. Thomas Co., Philadelphia, Pa.; American Hospital Supply Co., Chicago, Ill.

† Ketone testing reagents: Acetest Tablets, Ames Co., Elkhart, Indiana; Acetone Test Powder, Denver Chemical Co., New York.

In patients with long-established diabetes who show signs of only moderately severe acidosis the initial dose of insulin should approximate the usual total daily dose. In the presence of infection or with severe acidosis the initial dose should be at least double the usual total daily dose. One third of the initial dose may be given intravenously, two thirds subcutaneously.

During the first 6 to 18 hours, or until the urine is acetone-free, insulin should be administered hourly to two-hourly, in amounts around one fifth that chosen for the initial dose. The continuing dosage of insulin should be guided by frequent tests of the urine for sugar and ketone, and of the blood plasma for ketones. The total dosage of insulin given within 12 to 24 hours, before ketones disappear from blood and urine, may vary widely, but is usually from 20 to 50 units in infants, and from 100 to 400 units in older children.

Parenteral Fluids

A regimen of parenteral fluid administration designed for therapy of diabetic acidosis, instituted at the Children's Hospital two years ago, has been uniformly successful in correcting deficits of fluid and electrolyte in a number of patients with moderate to severe acidosis. The regimen has proved simple to administer and has resulted in rapid return to normal electrolyte balance with no evidence of accumulation of excesses. As with all such programs, it is designed for use as a guide, to be modified as necessary to fit special situations.

With this regimen the total volume of fluid administered in the first 24 hours of treatment approaches 4020 milliliters per square meter. To supply calories, replenish glycogen and guard against insulin reactions, up to 200 gm. per square meter of glucose are given. Sodium intake as sodium chloride amounts to 280 mEq. per square meter (equivalent to about 1860 ml. of isotonic saline solution), with additional amounts, as sodium bicarbonate or sodium lactate, given as needed to correct the acidosis. The potassium intake in the first 24 hours is close to 80 mEq. per square meter.

For convenience in planning the therapy the day has been divided into six-hour periods. During the first six hours fluid is infused at a rapid rate to give large amounts of sodium chloride and relatively small amounts of glucose. During the second six hours the rate of infusion of fluid and sodium chloride is decreased and the glucose intake increased. During the third six hours only glucose solution is given. This infusion may be continued during the fourth six hours, or, more usually, the infusion is discontinued at this time, and fluids are given by mouth. The potassium replacement is distributed equally over all the six-hour periods. Early infusion of potassium in the amounts used, even in cases

in which the serum potassium level is initially elevated, has not resulted in complications attributable to hyperkalemia.

An outline of the plan of treatment, including insulin dosage, is given in Table 19. After the initial administration of insulin and infusion of normal saline solution, designed to improve circulation, intravenous fluids consisting of isotonic saline, 5 or 10 per cent glucose, potassium as chloride or phosphate, and sodium as bicarbonate or lactate are given at the rate of 300 ml. per square meter per hour over the first six-hour period. Use of alkalinizing salts is limited to cases in which the serum carbon dioxide content is less than 10 mEq. per liter. The amount given is that necessary to raise the carbon dioxide content to 15 mEq. per liter. This amount of correction will usually bring the serum pH to approximately a normal value; the serum carbon dioxide content rises further as renal function improves and ketonemia is reduced. Alkali may be given as commercially available 7.5 per cent solution of sodium bicarbonate or as sixth-molar sodium lactate solution according to the following formulas:

Dosage per kg. body weight		elevates serum CO_2 content:
0.058 gm.	$NaHCO_3$	1 mEq./L.
4.2 ml.	M/6 sodium lactate	1 mEq./L.
0.026 gm.	$NaHCO_3$	1 vol. %
1.8 ml.	M/6 sodium lactate	1 vol. %

During the second six-hour period the rate of infusion is reduced to 150 ml. per square meter per hour and the intake of glucose increased by infusing the normal saline in 5 per cent glucose and by giving additional 10 per cent glucose. Potassium is added to the fluids in the amount of 20 mEq. per square meter, usually as a solution of potassium chloride containing 2 mEq. per milliliter.

By the end of the first 12 hours of treatment all the sodium and chloride needed for replacement has been given (288 mEq. per square meter), together with half of the estimated potassium requirement. At this stage the patient should be well hydrated, the severity of the acidosis greatly reduced, and the degree of ketonemia diminishing. Insulin should, by now, be fully effective in lowering blood glucose levels, and care should be taken that hypoglycemia does not occur.

During the third six-hour period, fluid can be given at the "maintenance" rate of 80 ml. per square meter. This infusion may be either 5 or 10 per cent glucose with potassium added in sufficient quantity to supply 20 mEq. per square meter. By this time sufficient improvement usually occurs so that the patient can take fluids orally, preferably those containing potassium. If so, the intravenous infusion may be discontinued during the last six hours. Otherwise therapy for the fourth period should be the same as for the third period.

This scheme of treatment is designed for the patient with moderate to

severe acidosis, with or without coma, but without the serious complications of severe shock or relative oliguria or anuria. For patients with severe shock the initial infusion of 360 ml. per square meter of normal saline may be profitably given as plasma or a plasma expander; or those solutions may be given as a separate infusion during the first six-hour

TABLE 19. *Insulin and Fluid Therapy in Diabetic Acidosis*

	INSULIN (Crystalline or regular, unmodified)	
First dose	In known diabetic—equal to usual daily dose	
	In new diabetic—40–60 units/M^2 body surface	
	Dosage should be greater if infection is present or if acidosis is severe	
Further dosage	Approximately $\frac{1}{5}$ the initial dose every 1 or 2 hours	
	FLUID	
Initial infusion, to improve circulation	Isotonic NaCl, 360 ml./M^2 in 30–45 minutes	
First 6 hours after initial infusion	Isotonic NaCl or Isotonic NaCl in 5% glucose	1200 ml./M^2
	Glucose, 5 or 10% solution $NaHCO_3$ or Na lactate, q.s. to raise serum CO_2 content to 15 mEq./L.	600 ml./M^2
	Potassium, as chloride or phosphate, 20 mEq./M^2	
	(Total fluid, 1800 ml./M^2; 300 ml./M^2/hr.)	
Second 6 hours	Isotonic NaCl in 5% glucose	300 ml./M^2
	Glucose, 10% solution	600 ml./M^2
	Potassium, as chloride or phosphate	20 mEq./M^2
	(Total fluid, 900 ml./M^2; 150 ml./M^2/hr.)	
Third 6 hours	Glucose, 5 or 10% solution	480 ml./M^2
	Potassium, as chloride or phosphate	20 mEq./M^2
	(Total fluid, 480 ml./M^2; 80 ml./M^2/hr.)	
Fourth 6 hours	Same as third or Discontinue intravenous fluids if patient is taking fluids by mouth	

period. In such cases the total volume of fluid given should remain the same; but if plasma is given, the volume of isotonic saline should be reduced by an amount equal to half the volume of plasma administered. In cases in which blood pressure has not responded to these measures intravenous l-norepinephrine has been used with success.

If oliguria or anuria exists, great care must be exercised in the administration of fluid. In such circumstances it is wiser not to attempt to hydrate the patient completely. Fluid and electrolyte losses should be replaced only partially on the first day. Potassium should be withheld unless overt signs of potassium depletion are present. Subsequently when partial hydration is effected, fluid intake should be adjusted to cover urinary plus insensible water losses with intake of sodium and potassium kept low.

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Elland Avenue and Bethesda
Cincinnati 29, Ohio

FLUID THERAPY IN RENAL DISEASE

WILLIAM B. WEIL, JR., M.D.

WILLIAM M. WALLACE, M.D.

The primacy of the kidney's role in the regulation of the volume, distribution and ionic concentration of the body fluids is well known and has been discussed elsewhere in this volume (p. 43*ff*.). In the light of this central function it is perhaps surprising to find that in many diseases of the kidney homeostasis of the body fluids, from the functional standpoint at least, is relatively well maintained despite the fact that only vestiges of renal tissue remain. Often the compensatory adjustments that occur in response to destruction of renal tissue are so complete that no clinical disorders of water, sodium and potassium metabolism are evident. Short of the terminal phase, it is only when such compensatory mechanisms fail that such disorders appear and account for the major clinical findings. These disorders of salt and water metabolism accelerate the course of the disease and may be the primary cause of death.

Physiologic as well as clinical experiment and observation during the past 30 years have shown that Cushny's concept of the mode of action of the kidney, though an oversimplification, in essence describes the mechanisms by which this organ regulates the volume and composition of the body fluids. In this conception a volume of fluid equal to 15 times the extracellular fluid is subjected to daily filtration through the glomeruli and retrieval by the combined tubular and collecting duct systems to the extent of over 99 per cent of the quantity filtered. The tubular and collecting duct system can be thought of as infusing the body with an ideal fluid from which it has removed surplus or undesirable solutes and water. In this process the mechanisms of hydrostatic filtration, active cellular transport, passive diffusion along the gradients created

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by cellular transport and countercurrent flow in the parenchymal blood vessels are utilized to accomplish the end result. The kidney is, within generous limits, capable of disposing of surplus water and solute or, conversely, of conservation of these essential substances. *It cannot make up deficits,* however. The obvious but little known and studied reflexes governing thirst and appetite bear the responsibility for replacement. The volumes of intracellular and extracellular fluid appear to be the most important physiologic variables around which intake and excretion are coordinated in the critical regulation of body fluid homeostasis.

The net effective reserve of the kidney alone is great. When combined with an intact system regulating intake, its reserve is enormously extended. This accounts for the relative lack of life-endangering disturbances in body fluid physiology until renal parenchymal destruction is far advanced. Indeed, it is only when consciousness is so disturbed, as by uremia or renally induced encephalopathy, by lack of access to water or the strength to obtain it or by copious losses through vomiting and diarrhea that the physician must intervene and attempt to manage the body fluid economy by artificial means. Interference with intake compensation is particularly frequent and severe in young infants by virtue of their helplessness and inability to communicate their needs.

TYPES OF RENAL PATHOLOGY

Viewed from the standpoint of fluid therapy, three general type of functional renal pathology may occur. These rarely occur singly, but more often as a variable mixture with one or the other type predominant, often in variable sequence and recombination.

The most common of these in pediatric experience is *imbalance between filtration at the glomerulus and tubular reabsorption.* Functional and anatomic abnormalities resulting in changes in relative activity of these two components of excretion may become so great that retention of water and salt occurs and edema ensues. This is the most prominent disturbance of fluid metabolism in acute glomerulonephritis and nephrosis. Much evidence indicates that such glomerulotubular imbalance at times represents an adaptive response by means of which critical depletion of blood volume is averted in the face of disturbance in the vascular-extracellular filtration equilibrium.

A second type of disorder appears in *progressive nephron-destroying disease,* such as glomerulonephritis, certain instances of the nephrotic syndrome, chronic pyelonephritis and obstructive uropathy. Such a process leads to progressive reduction in the breadth of control that the kidney exercises over its function of conservation in the presence of deficits and disposal in the presence of surpluses. If the process proceeds far enough, the capacity of the kidney to concentrate or dilute the

urine becomes lost, and the specific gravity becomes fixed at that of glomerular filtrate (*isosthenuria*). Loss of ability to concentrate the urine usually precedes the loss of diluting power. No entirely convincing explanation for the mechanism of the isosthenuria of chronic renal disease has been advanced.[9] The most usually accepted explanation is that it is identical with the decrease in urine specific gravity seen in the normal person required to excrete a large load of solute. In present day terminology it therefore represents an "osmotic diuresis." In the normal person renal mass is constant, but the load increases; in renal disease renal mass decreases, while total load remains the same. As the filtering surface is decreased by progressive disease, the plasma urea concentration rises and the load per nephron is increased in exactly the same fashion as in solute loading with a normal filtering surface. Favoring such an explanation are the observations of Hayman and associates[5] and of Bradley[1] that events which suddenly tend to lower glomerular filtration rate in subjects with renal failure may be accompanied by apparently paradoxical increases in urine specific gravity.

Initially, the loss of concentrating power is associated with increased urine volume, while the sensation of thirst meters an appropriately increased fluid intake. The decreasing renal mass operates at greater speed to offset its reduced efficiency. As filtering surface decreases, substances such as urea, potassium and phosphate, which are carried at low plasma concentrations, yet are abundantly present in the intake, fail to be adequately excreted despite the diuresis, and accumulate in the body fluids. On the other hand, the essential elements of plasma structure, such as sodium, chloride and water, which are present in high concentration in extracellular fluid and often at low concentration in the intake, tend to be lost to the body in the accelerated process of urine formation. Study of the data shown in Table 20 will make this important concept clear. Thus, as renal failure advances, the patient runs a twofold danger: i.e., loss of water and salt, upon which the circulatory integrity depends, and the accumulation in the body fluids of substances inimical to proper function of many tissues. The clinical state ultimately becomes one of dehydration and uremia.

The third general type of disturbance is the *complete cessation of urine formation*. This may occur in all forms of renal disease as either a transitory or terminal event. However, the anuria or severe oliguria associated with ingestion of nephrotoxic substances, following improper transfusion, episodes of hypotension and severe bodily injury presents major therapeutic problems in fluid therapy. The renal and body fluid physiology in such instances will be discussed below.

A fourth, relatively rare type of renal disturbance that is of importance for conceptual thinking about renal disease and its therapy is that of *specific tubular defects* resulting in impairment of the excretion

TABLE 20. *The Relation of Filtration to Load for Sodium, Phosphorus and Urea*

GLOMERULAR FILTRATION RATE		MILLIMOLS FILTERED PER DAY			
% of Normal	Liters/Day	Na (140 mEq./L.) 140 mM./L.	HPO_4 (4–8 mg.%) 1 mM./L	2 mM./L.	Urea N (11 mg.%) 4 mM./L.
100	180	25,000	180	360	720
75	135	19,000	135	270	540
50	90	12,500	90	180	360
40	72	10,000	72	144	288
30	54	7,500	54	108	216
20	36	5,000	36	72	144
10	18	2,500	18	36	72
5	9	1,250	9	18	36
Daily load (mM.)		40–180	20–60		200–600

Adapted from Gamble.[4]

When the serum concentration of a substance is high in relation to load (Na), the filtration rate can be greatly decreased and the quantity filtered still exceed the load. When the load is appreciable, but the serum level low (HPO_4), the load will exceed the amount that can be filtered as filtration rate falls. In the example shown, when a large load is ingested, the capacity to clear it will be exceeded when the glomerular filtration rate is less than one third of the normal. Retention results, and the serum concentration rises. Doubling of the serum concentration doubles the amount filtered, and no further retention occurs until filtration rate is half of the previous value. If the ratio of load to serum concentration is still higher (urea), retention of this material in the body would be expected to occur before that of a substance with a lower ratio (HPO_4).

of certain ions or un-ionized solutes. Specific tubular transport defects for water, hydrogen ion, phosphate, potassium, calcium, glucose and amino acids have been described. These may be congenital in origin or acquired during the course of more common renal disease. Certain of these may so disturb over-all renal function that they lead to total renal failure. In so-called renal hyperchloremic acidosis, in which the primary disability lies in inability to acidify the urine, the prolonged excretion of an alkaline urine and the secondary hypercalciuria eventually lead to renal parenchymal destruction.

RENAL COMPENSATORY MECHANISMS

It is important for the physician to recognize and understand the compensatory mechanisms that come into play in renal disease. Many of them at first glance appear to be inappropriate and even harmful, but, upon closer examination of their true functional and biologic significance, are shown to be lifesaving or life-prolonging compensations. Thus the polyuria and polydipsia of advanced renal disease represent compensatory operations of the utmost importance. Interference with fluid intake under such conditions either intentionally or because of lack of ability of the patient to obtain water accelerates the course of renal failure and rapidly brings on disorders of fluid homeostasis. Voluntary ingestion of large quantities of salt in patients with certain types of renal disease represents a type of compensation. The high concentration of substances such as urea, phosphate and potassium in the blood of patients with renal disease represents, in part, an automatic type of compensation by means of which excretion by the failing kidney is enhanced. For example, rapid reduction of high blood urea concentrations by means of the artificial kidney can lead to so-called post-dialysis oliguria.[6] As has been noted above, even the edema that appears in certain types of renal disease can be considered to represent an adaptive compensatory response.

PRINCIPLES OF FLUID THERAPY IN RENAL DISEASE

The principles of fluid replacement and maintenance are no different in renal disease than in any other clinical situation requiring such therapy. Their application in actual practice is more difficult, however, and facile regimens prescribing fluid administration are more likely to fail or to do harm. In patients with intact renal function in whom deficits of water and electrolytes have occurred and are occurring, high precision in diagnosis and therapy is not as essential as in the patient with renal failure. The patient with normal renal function can dependably select and reject orally or parenterally administered water and electrolyte when

given within the known capacity of renal adjustment. In the patient with advanced renal disease the clinician must attempt to mimic the metering and adjusting abilities of the kidney, a task that is often discouraging and always humbling.

Talbot and associates[12] have discussed in detail the respective "floor" and "ceiling" representing maximum excretory ability and maximum conserving ability of the normal kidney and of the kidney in renal disease.

> Up to the present time, no procedure has been devised that permits one to define all a given person's safe working ranges in a simple, easy manner. On the other hand much useful information can be had by measurement of rates of urinary output of water and solutes when the patient is first seen or while he is eating in his customary manner and considering them with relation to his homeostatic status at that time.

These statements emphasize the need for careful quantitative observation in the management of the patient with renal disease requiring artificial support of his fluid and electrolyte exchanges. Careful attention to changes in body weight, to urine volume, to the changes in the serum concentrations of sodium, potassium, bicarbonate, pH, phosphate and urea is essential for maximum effectiveness of management. When intakes of ions are known or when they are minimal or zero, measurement of the total quantities of sodium or chloride or potassium in the daily urine may be of value in guiding decisions for future therapy.

MANAGEMENT OF FLUID THERAPY IN SPECIFIC DISEASES

Acute Glomerulonephritis

The quantity of fluids to be administered to the patient with acute glomerulonephritis has always been a matter of controversy. Practice has swung between the absolute interdiction of fluid to that of forcing relatively large quantities. The former was predicated upon the notion that absence of a fluid intake would put the kidney at rest and favor healing, the latter on the concept that urine volume could be increased and favor removal or at least dilution of undesirable metabolites. Neither has any rationale in the light of present knowledge of renal function in acute nephritis, and both these extreme procedures have been shown to increase mortality. Except under unusual circumstances, thirst can be dependably relied upon to guide fluid intake.

When edema and hypertension are present, moderate salt restriction is of value. The ordinary diets served in children's hospitals contain approximately 5 gm. of salt a day when no added salt is allowed (no salt shaker on the table). A salt-poor diet (1 to 3 gm. per day) can be easily prepared by hospital dietary services without resorting to special food preparation. Diets with a salt content in this range are adequate for children with edema and are well taken. To go below 1 gm. per day

requires special preparation and produces diets that no child can be motivated to eat. Except under special conditions, rigid salt restriction has no place in the management of edematous states in children, since it often results in salt depletion even in the presence of edema (see below under The Nephrotic Syndrome). When extreme hypertension, cardiac decompensation or anuria is present, the fluid regimen described below under Acute Renal Failure should be followed.

The Nephrotic Syndrome

The statements made above as to the use of a fluid intake guided by the child's sense of thirst and as to sodium intake are applicable with equal force to the edematous phases of the nephrotic syndrome.

Certain urgent special conditions affecting fluid and electrolyte homeostasis may occur during the prolonged course of this disease. Their recognition and proper therapy are essential, since they may lead to death in a child who would otherwise recover completely. During the era when extreme salt restriction (below 1 gm. per day) was widely practiced in the management of nephrotic edema, it soon became evident that salt depletion, even in the presence of abundant edema, could regularly occur. The clinical syndrome of salt depletion in nephrosis tended to be overlooked because these children were edematous and regarded as surfeited with salt. In an absolute sense this was true. However, the primary problem was the accumulation of water in excess of sodium and the apparent unavailability of the edema fluid for rapid redistribution in the face of falling circulatory volume. Even in the absence of formal salt restriction such events may take place. The profound anorexia present in these children can lead to vanishing salt intakes. Episodes of diarrhea and vomiting, the procedure of paracentesis and even spontaneous or steroid-induced diuresis can lead to symptomatic salt depletion with accompanying circulatory insufficiency. Discussion of the physiologic mechanisms involved in the genesis of this condition is beyond the scope of this paper. Suffice it to say that they are concerned with the automatic systems regulating body fluid volumes and distributions. These have been reviewed in readable detail by Strauss.[11]

The impending circulatory failure is usually brought to the attention of the physician by the appearance of restlessness, weakness, orthopnea and anxiety in the child. Close examination of the fully developed syndrome will show a sunken-eyed child with a dry mouth. Often the child is thirsty, but has been denied water by the attendants because of his anasarca. Examination of the heart shows a rapid rate, and often bizarre murmurs have appeared since previous examination. The blood pressure is low or at times unobtainable. Such patients are critically in

need of salt replenishment. It has been our procedure to begin immediately the infusion of isotonic saline solution or lactated Ringer's solution in amounts equivalent to 2 to 3 per cent of body weight (20 to 30 ml. per kilogram of body weight). This quantity of fluid should be given in a period of two to four hours, depending upon the urgency of the situation; 25 gm. of concentrated human serum albumin can advantageously be added to this first quota of fluid. Determination of the plasma concentration of sodium, potassium and carbon dioxide should be carried out as soon as feasible. Plasma sodium concentration is usually below 130 mEq. per liter, often below 115 mEq.

After the initial infusion the clinical state should be completely reevaluated. If signs of circulatory deficit still exist, the infusion of isotonic salt solution should be continued until a further 20 to 30 ml. per kilogram have been given. The second half of this quota of fluid should be given more slowly (six to eight hours). At times hyponatremia and suggestive circulatory failure may develop in patients with the nephrotic syndrome without preceding salt-depleting events. In such patients the use of hypertonic (3 per cent) salt solution may be indicated after careful consideration of their condition. The method of calculation of the quantity of such solution needed is given below under the section on Acute Renal Failure.

The development and treatment of acute hyponatremia in a child with the nephrotic syndrome are illustrated in the following case report.

P.S., a 5½-year-old white girl with the nephrotic syndrome, had 3 previous admissions to this hospital. Two of these were characterized by episodes of hyponatremia which responded to administration of hypertonic salt solutions. On this admission she had symptoms of abdominal pain and nausea, as she had had with the 2 previous episodes of hyponatremia. At the time of admission her serum sodium was 137.5; carbon dioxide, 27.7; potassium, 5.7 mEq. per liter; pH, 7.47; blood urea nitrogen, 17 mg. per 100 ml. Her weight was 22.4 kg. Urine specific gravity was greater than 1.040. Physical examination was negative except for mild periorbital edema. She had been on a low salt intake at home, and this was continued in the hospital. She was given clear fluids ad lib. during the first 24 hours. The next day her serum sodium was 125; serum chloride, 92; serum potassium, 5.5; carbon dioxide, 25.1 mEq. per liter; and pH, 7.39. Her weight was 24.4 kg., and she appeared acutely ill with signs and symptoms suggesting shock and cardiac failure.

At this time balance studies were started which were continued for 5 days. That the patient was initially dehydrated is indicated by the hemoglobin of 16.8 gm. per 100 ml., and red blood cell count of 5.74 million per cubic millimeter. After the gain in weight her hemoglobin was 10.7 gm. and her red cell count 3.86 million. On the first and second days of the balance study she was given 300 ml. of hypertonic saline (500 mEq. per liter), an amount calculated to raise her sodium 10 mEq. per liter each day. At the end of this time her serum sodium was 139.5; chloride, 107.4; and potassium, 4.8 mEq. per liter.

Her course was uneventful after this, and the balance study was discontinued at the end of the fifth day; the serum sodium was 141 and the serum chloride 107.3 mEq. per liter. The cumulative balances for sodium, chloride, potassium and water are illustrated in Figure 23. The retention of sodium and chloride was just sufficient to render the retained water isotonic. There was no significant change in potassium. The calculated changes in total body water, extracellular and intracellular fluid volumes

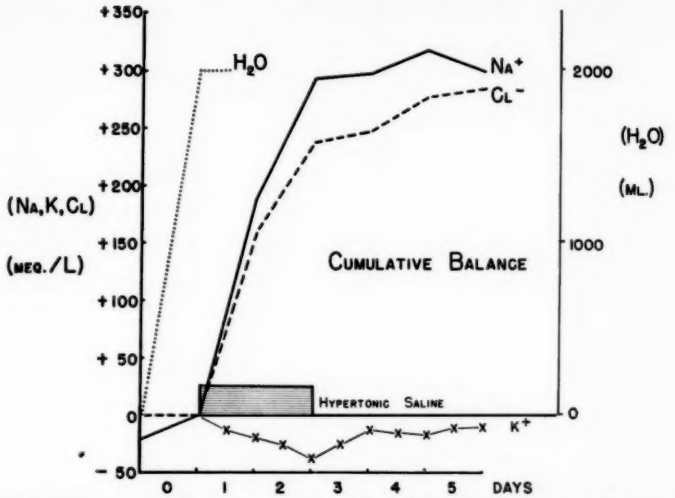

Fig. 23. The cumulative balance of sodium, chloride, potassium and water in patient P.S. The ordinates for the balance of electrolytes on the left and for water on the right have been arranged so that 1 liter of water is equivalent to 150 mEq. of an ion. The balance for water after the second day is not shown, but remained essentially level throughout the remaining days of the study. Day 0 is so indicated because only estimates are available for the electrolyte balance on that day.

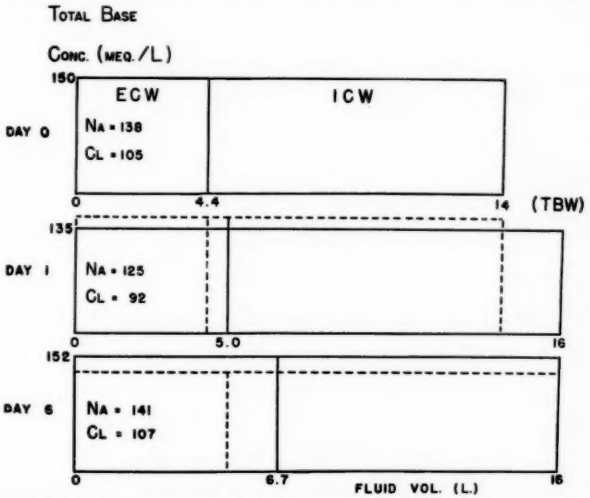

Fig. 24. The fluid and electrolyte shifts in patient P.S. The volumes have been plotted along the abscissa and the total cation (Na + 10) concentration along the ordinate. The area then represents the absolute amount of cation present in each compartment. The interrupted line on the diagram for the beginning of Day 1 represents the status at the beginning of Day 0. On Day 6 the interrupted line represents Day 1.

and the concentration of electrolytes are shown in Figure 24. As can be noted in the period when she became hypotonic, she had an expansion of body water of 2 liters. This was divided between the extracellular and intracellular fluid in approximately proportional amounts. With hypertonic sodium chloride the excess fluid was shifted entirely to the extracellular space, and this shift of fluid created the rise in ionic concentration of the intracellular fluid; the administered sodium chloride produced the rise of concentration in the extracellular fluid.

The pattern this child showed indicates that this episode occurred when she became dehydrated and then attempted to rehydrate herself with inadequate sodium chloride intake. A similar course was noted on a subsequent admission. This suggests that, although she was edematous, she was dehydrated in terms of intravascular fluid. The resultant thirst led to expansion of her fluid volume; lacking adequate salt, she became concomitantly hypotonic. Her urine output before the gain in weight was of small volume and high specific gravity, but low in sodium and chloride concentration, a response which would seem appropriate under the circumstances.

Chronic Renal Failure

Urinary tract obstruction with hydronephrosis is the commonest cause of chronic renal failure in children. Less frequent causes are nephritis, nephrosis, chronic pyelonephritis and anaphylactoid purpura. The general nature of the disturbed physiology has been outlined above. Many of these children may have appeared to be well and their only symptom to have been the characteristic compensatory polyuria. Bouts of infection, gastrointestinal upsets and even hot weather interfere with fluid intake and break the compensatory processes. Dehydration and acidosis quickly follow, renal function is further depressed, and the ensuing exacerbation of the uremia further increases the difficulty in maintaining a fluid intake. At this point parenteral therapy becomes an urgent need. It is essential that the physician take an optimistic view of therapy at this time. It is often impossible to predict whether the current episode is only one of decompensation or a terminal event. Only after therapy has been carried out can a better view of prognosis be had.

Determinations of serum concentrations of sodium, potassium, bicarbonate and phosphate are essential guides to therapy and of more than academic value. If dehydration, oliguria, hypotension and a low serum sodium concentration are present, parenteral fluid therapy as described above for salt depletion in the nephrotic syndrome should be started. Once dehydration is repaired, maintenance fluid therapy at the rate of 1800 to 2000 ml. per square meter per 24 hours, using solutions containing 40 to 50 mEq. per liter of sodium, should be continued. Appropriate solutions can be prepared by mixing sixth-molar sodium lactate, isotonic sodium chloride and 5 to 10 per cent glucose solutions in the proportion of 1:2:9 or 1:2:6. Blood pressure, cardiovascular status, urine volume and body weight must be carefully observed at intervals. If adequate urine volumes are not established within 48 hours by such a regimen, fluid therapy should revert to the more restricted type as described below under Acute Renal Failure. In patients who are normo-

tensive and oliguric and have normal serum sodium concentrations, dilute solutions as described above should be given until they are again able to take an oral intake or until it is certain that reasonable urine volumes will not be established.

In general, such patients will present with either normal or high plasma potassium concentrations. Potassium should not be given in the parenteral fluids. Occasionally patients are encountered with hypokalemia at the onset, or, more frequently, they become hypokalemic after dehydration has been repaired and a urine volume established. In these instances potassium should be added to the dilute electrolyte solutions in sufficient quantity to make a potassium concentration of 15 to 25 mEq. per liter. Measurement of the serum potassium concentration and frequent observation of the electrocardiogram can be used to assess the effectiveness of this therapy and guard against excess.

As dehydration and acidosis are corrected, tetany may appear, particularly in patients with high serum phosphate concentrations. The addition of 10 ml. of a 10 per cent solution of calcium gluconate to each 250 ml. of the infusion will usually correct, at least temporarily, this abnormality. If, after hydration, the hemoglobin concentration is below 7 gm., small transfusions of 50 to 100 ml. of whole blood or packed cells should be given every 12 to 18 hours until adequate correction of the anemia is obtained.

Acute Renal Failure

Acute, temporary, functional failure of the kidney may result from a number of events, e.g., transfusion reaction, hypotension, extensive tissue injury, chemical poisoning, vascular spasm of acute glomerulonephritis. Specific medical therapy is the primary consideration in the management of these cases, but is not within the scope of this paper. The fluid therapy is essentially the same in all cases and depends on the stage at which the patient is seen.[8]

There are generally three stages in the process of acute renal failure: preoliguric, oliguric and diuretic. The preoliguric period is the time between the event producing the syndrome and the actual beginning of oliguria. This stage, which may last several hours to several days, is characterized by decreasing glomerular filtration and decreasing renal blood flow. In those cases resulting from toxic materials the degenerative changes take place in the tubules, presumably because of the reabsorption of water and resultant concentration of the toxic substance at this site.

The second stage is that of oliguria with daily urine outputs below 100 to 200 ml. per day and lasting from 1 up to 30 days, but generally of 10 to 14 days' duration. During this period glomerular filtration rate is

extremely low, and most of the filtered fluid passively diffuses back through the damaged tubules. Healing of the tubular lesion begins quickly and proceeds throughout this time.

Since adequate calories can rarely be supplied to the patient, considerable tissue destruction will occur. This results in the accumulation of nitrogenous waste products, potassium and the fixed anions phosphate and sulfate. Progressive azotemia, hyperkalemia and metabolic acidosis are the chemical measures of this process. The hyponatremia and edema which may occur are generally considered to be the result of too large a fluid intake rather than of internal shifts of electrolyte or endogenous water production.

Early in the diuretic period tubular regeneration is still incomplete. Although the volume of urine may be large, the tubules are unable to conserve electrolytes, potassium is secreted at a high rate, and excessive back diffusion of urea and other nitrogenous metabolites will occur.[2] In this situation the patient's condition will usually continue to deteriorate, and many of the deaths have occurred at this time. In five to seven days the large urine volume decreases somewhat, indicating that most of the functional repair of the tubules has occurred. Some improvement in tubular function will continue for many months.

With the exception of acute glomerulonephritis, it would seem likely that during the period preceding the oliguria the severity of the subsequent stages can be modified by production of a large volume of urine. Presumably this can dilute the toxic agent at the site where damage occurs, as well as continue the excretion of any offending material. Therefore, if the patient is seen shortly after an incident likely to lead to oliguria, fluid restriction should not be attempted until after any dehydration has been repaired and a water load administered. During the preoliguric period blood, plasma or plasma substitutes may be required for the treatment of shock. Dehydration may be corrected by administration of saline or Ringer's lactate solution in a volume equivalent to 2 to 7 per cent of the body weight, depending on the degree of dehydration present. Any additional fluid should be given at the rate of 1500 ml. per square meter per day, and this should be primarily glucose or fructose solutions, including 100 to 200 ml. per square meter per day of saline or Ringer's lactate solution. Then, only when oliguria becomes obvious, should intake be limited.

If the patient has an established oliguria when first seen or when this stage of the process occurs, fluid management can be divided into five areas:

1. The *volume of fluids* required each day will be equivalent to the sum of (*a*) insensible loss from the skin and lungs, (*b*) any gastrointestinal losses, and (*c*) the urinary output, minus the water formed by (*d*) the oxidation of protein, fat and carbohydrate, and (*e*) the water

released by the disruption of tissue cells inherent in the catabolic state which is always present.

(*a*) The insensible loss from skin and lungs will average about 500 ml. per square meter per day. This will be increased in the presence of fever by 75 ml. per square meter per degree centrigrade.

(*b*) The losses for the gastrointestinal tract can be minimized by avoiding oral intake unless it is well tolerated by the patient.

(*c*) The urine output during this phase of the process increases gradually on successive days, and reasonable estimates can be made from the preceding 24-hour volume.

(*d*) Water resulting from the oxidation of ingested food or body fat, carbohydrate and protein amounts to about 0.1 ml. per calorie or about 100 ml. per square meter per day in the average patient.

(*e*) The destruction of 1 kg. of muscle provides about 250 gm. of protein, 750 gm. of water and, when fully metabolized, 1000 calories. The administration of calories parenterally or orally will reduce the rate of tissue catabolism so that no practical figure can be given for the amount of fluid released in this manner. To provide calories at a reasonable level, the use of 10 to 30 per cent carbohydrate solutions is recommended.

The most useful determination in calculating the total fluid requirement is the patient's weight, which should fall about 10 to 20 gm. per kilogram per day if the proper amount of fluid is being given.

2. *Azotemia* is best handled by minimizing protein catabolism and by restricting protein intake. These goals can best be achieved by the use of hypertonic carbohydrate solutions and by oral administration of carbohydrates and fats.

3. *Hyperkalemia* may be ascertained by chemical analysis of the serum and by electrocardiography. The latter method would appear to be more useful in judging the seriousness of the situation. The loss of potassium from cells can be minimized with the use of hypertonic carbohydrate solutions. No additional potassium should be given during this period. Carboxylic acid type resins in the sodium cycle (Lilly) can be given orally or rectally as a 10 per cent mixture in water and using 5 to 10 gm., 2 to 4 times a day.[3] The amount required can be judged by serial electrocardiograms and determination of the serum potassium.[10, 13]

In an acute situation temporary measures which can be used until more definitive treatment can be instituted include hypertonic saline, 100 to 300 ml. of 3 to 5 per cent solution; 10 to 50 cc. of 10 per cent calcium gluconate given slowly intravenously; and 50 per cent glucose. Insulin with the hypertonic glucose may be of value, but should be used cautiously, since hypoglycemia can be produced in this manner.

4. *Hypotonicity as reflected by hyponatremia* may occur even if all the foregoing measures are carried out successfully. Treatment is required

only if there are symptoms of water intoxication referable to the low solute concentration in the serum. These will rarely occur until the serum sodium is below 120 mEq. per liter. Then 3 per cent sodium chloride solution should be used in an amount necessary to raise the plasma sodium concentration to 130 to 135 mEq. per liter. The amount required is calculated as follows:

$$\text{mEq. Na required} = (132 - \text{serum Na}) \times 0.6 \times \text{body weight (kg.)}$$

One milliliter of 3 per cent sodium chloride solution contains 0.5 mEq. of sodium.

5. *Hypocalcemia* may be a problem in this period, but is more likely to lead to problems during the phase of diuresis. The use of 10 per cent calcium gluconate intravenously in doses of 20 to 100 cc. per day may be required to prevent the signs of tetany.

Although extracorporeal dialysis is not a problem of fluid therapy, this important technique is often the most effective method for correction of electrolyte disturbances as well as reduction of the azotemia and the concomitant depression of the sensorium.[7]

The diuretic phase builds up over a period of a day or two, and then replacement of fluid, sodium, potassium and calcium presents the problem. One can assume a sodium concentration of 100 mEq. per liter and a potassium concentration of about 30 mEq. per liter in the urine, but analysis of these constituents would be useful. During the early period the concentration of sodium and potassium in the urine remains fairly constant in any individual patient. One should not attempt to replace all the sodium, because there is usually an excess in the body when diuresis begins.

SUMMARY

Disorders of fluid and electrolyte metabolism accelerate the course of renal disease and may be the primary cause of death. Proper application of parenteral and oral fluid maintenance and repair can often be the means for restoring the natural compensatory mechanisms and extending the life and comfort of the patient.

In the patient with competent renal function the kidney aids therapeutic efforts by disposing of surpluses and by conserving when there are deficits. In the patient with renal disease the range of such adjustment is greatly narrowed. In contrast to fluid therapy in patients with normal renal function, fluid therapy in patients with reduced function is dependent to a greater extent upon intimate knowledge of the pathologic physiology occurring.

The nature of the fluid and electrolyte disturbances in renal disease,

the compensatory mechanisms invoked by the body and certain basic approaches to therapy have been outlined.

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THE METABOLIC REACTION TO INFECTIOUS DISEASE

ROBERT E. GREENBERG, M.D.

LYTT I. GARDNER, M.D.

A fever is a disease which affects the whole system. . . . It affects the circulation, the absorption, and nervous system. It affects the skin, muscular fibres, and the membranes. It does not however affect the various parts of the system uniformly and equally. . . . This has given great ambiguity to this disease.—George Fordyce, M.D.: *Dissertations on Fever,* Philadelphia, 1846.

During the past decade the important and socially significant advances in chemotherapeusis of infectious diseases have been paralleled by similar advances in understanding of fluid and electrolyte therapy. Information on maintenance needs and altered requirements in disease has been accumulated.

It has been said that some of the newly isolated viruses which are capable of infecting the human host are organisms in search of a disease. Similarly, some of the enigmatic changes in electrolyte structure during illness may themselves be responsible for no known disability to the patient. These instances suggest that investigation in both areas is becoming less disease-oriented and more concerned with the broader ecologic aspects of the terrestrial environment. Attention is now being directed to the alterations in the cellular metabolism of both the host and the infectious agent as they interact. Lwoff has commented on this concept of interaction between the infectious agent and the human body cell as follows:

At the onset of the nineteenth century, Pierre Bretonneau disentangled the doctrine of specificity of disease out of a terrific confusion of ideas and realized that the differ-

From the Department of Pediatrics, State University of New York, Upstate Medical Center at Syracuse.

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ences in the clinical and pathological pictures were due to differences in the nature of morbid causes. These were, later on, identified as microorganisms. A pathogenic microorganism, is, by definition, the agent or potential agent of a disease, the disease being the reaction of the organism toward the pathogenic agent. And it is known that sometimes, specific substances produced by the microorganisms are responsible for specific symptoms or syndromes. *But the active participation of the cells in the morbid process is of primary importance.*[27] [Authors' emphasis]

Thus we are at the stage in scientific development where the broad outlines of knowledge concerning infection and fluid and electrolyte metabolism have been worked out. At present relatively empirical applications of this knowledge allow restoration of the infected or altered organism to homeostatic equilibrium. However, it is in the microcosm of cellular metabolism that syntheses of knowledge relating the altered composition of body fluids and electrolytes in infectious diseases will become possible.

It is the purpose of this article to discuss the general features of infectious diseases and their effects on body fluid and electrolyte balance. We will briefly review specific findings indicated by recent investigations, and discuss their implications. The bibliography makes no attempt at completeness; only representative articles are referred to. The most common alterations in body composition during the course of infections have to do with factors either producing abnormal loss of fluid and electrolyte, such as in diarrhea, or significantly affecting certain homeostatic mechanisms, such as pulmonary or renal infections. Fluid therapy of these states is discussed in other clinics of this volume.

FACTORS COMMON TO INFECTIONS IN GENERAL

Stress Reaction

Selye observed that a great variety of stimuli appear, at least grossly, to produce a similar metabolic pattern. This pattern he described as follows (as applied to severe stress):

. . . The reaction consists of two more or less distinct phases. The transition between these is not always sharp and some of their manifestations may overlap, but generally speaking, it may be said that the following are characteristic of the first or shock phase: tachycardia, decrease in muscular tone and body temperature, formation of gastric and intestinal ulcers, hemoconcentration, anuria, edema formation, decrease in blood chlorides, acidosis, a transitory rise followed by a decrease in blood sugar, leukopenia followed by leukocytosis, and discharge of adrenalin from the adrenal medulla. This phase may last anywhere from a few minutes to 24 hours, depending on the intensity of the damage inflicted, but unless the termination is fatal, it is always followed by the counter shock phase. The latter is characterized by: an enlargement of the adrenal cortex whose cells show signs of increased activity, acute involution of the thymus and other lymphatic organs and a reversal of most signs characteristic of the shock phase. Thus, there is blood dilution and increase in blood volume, increase in blood sugar and blood chlorides, alkalosis, diuresis, and often a rise in body temperature.[38]

Moore[29] has documented a common pattern of fluid and electrolyte

change in injury, surgery and disease. By using surgery as the stress, a dilutional hypotonicity has been defined, characterized by a rise in serum K^+ and fall in serum Na^+ during the 36 hours following operation. This reflects a resultant of multiple factors producing a sodium-potassium shift from extracellular to intracellular spaces, a release of new sodium-free water from lysis of cells and fat, which, in turn, results in an increased blood volume and negative nitrogen balance. That the fall in serum Na^+ reflects transfer across cell membranes and hypotonic dilution is supported by well documented observations that there is salt and water retention following stress.[9]

It has proved increasingly difficult to study patients with infectious diseases in terms of body fluid and electrolyte composition, owing to the advent of specific antimicrobial and antipyretic therapy. There are a number of studies which indicate that fever and infection produce changes analogous to the postoperative response.[9] Soule et al.[41] noted a retention of water by the body as a whole during fever and release of this water after defervescence. In studying 52 cases of pneumonia Rutstein et al.[36] observed an increased mean plasma volume and mean "extravascular thiocyanate space" during the febrile phase of the infection.

That the adrenal steroids exert a "permissive" and not determinant effect on these metabolic aberrations has been stressed by Ingle[20] and Sayers.[37] This concept holds that the general role of the adrenocortical hormones in body economy is to act as general tissue hormones supporting the capacity of all tissues to adapt, rather than exerting an obligatory control upon any of the known metabolic processes. From this it would follow that increased "need" for adrenocortical hormones activates the adrenal cortex during stress—such activation serving to preserve homeostasis rather than creating a state of hypercorticism.[20] The basic biochemical and biophysical reactions into which the adrenal steroids enter have not yet been identified.

Various forms of stress, including infections, may likewise affect such biochemical reactions and thus determine the relative "need" for steroids. In cases of meningococcemia and meningococcal meningitis Klein[25] found high levels of corticoids in plasma, the lowest being 17 micrograms per 100 ml. in a case of meningococcal meningitis with vascular collapse. Kelley[24] has similarly reported high values for corticoids in the plasma in a variety of acute bacterial and viral infections, the mean value for 18 such patients being 32 micrograms per 100 ml. (controls, 12 micrograms per 100 ml.). Figure 25 depicts a conceptual scheme of what may be the response of plasma corticoids to the stress of infection.[14] It is indicated that levels above normal may be, in fact, inadequate to meet the homeostatic needs of the infected organism.

The translation of this concept to medical practice in the management of infectious disease remains, however, a most difficult task.

It would seem unlikely, as Conn et al.[5] point out, that stressful conditions, regardless of quality, intensity or duration, should evoke a rigid set of metabolic consequences. They compared the response of normal men to intravenous ACTH, typhoid H antigen and Piromen (a polysaccharide fraction obtained from Pseudomonas). The following reaction patterns were found: (1) Piromen produced a positive nitrogen balance and lack of the usual increased urinary uric acid excretion fol-

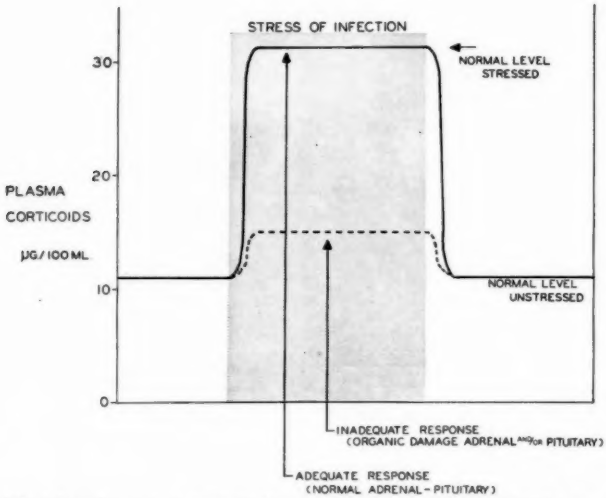

Fig. 25. Adrenal response to infection, using plasma corticoid levels as an index of adrenal activity. (From L. I. Gardner: Adrenocortical Metabolism of the Fetus, Infant and Child. *Pediatrics*, Vol. 17.)

lowing stress; (2) the response to pyrogens was delayed as compared to ACTH; (3) the metabolic pattern in response to pyrogens lasted longer than did the increased corticoid output; and (4) Piromen produced retention of both K^+ and Na^+, in sharp contrast to the pattern following either typhoid H antigen or ACTH. These results have been confirmed for Piromen by Wexler et al.[44]

The metabolic consequences of the total response to varying stimuli thus appear to be qualitatively as well as quantitatively different. These differences are, in part, due to different specific damaging effects of infections on cellular metabolic processes. Further, the "reaction to and repair of specific damage should be expected also to be specific."[5]

The importance of the nonendocrine aspects of stress has also been emphasized by Goldstein and Ramey.[17] Figure 26 represents an adapta-

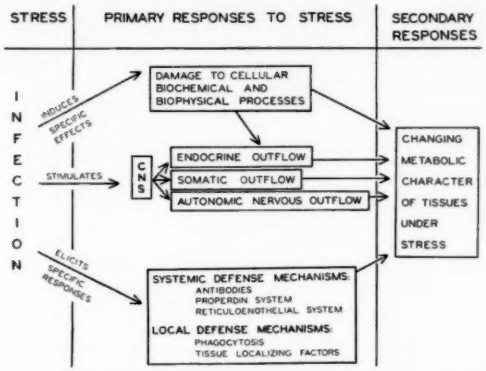

Fig. 26. Conceptual scheme of total body response to the stress of infection. The main purpose of this chart is the placement of the adrenal response in the perspective of a total body reaction.

tion of their scheme summarizing total body reaction to stress, in this case infection.

Fever

DuBois suggested that "fever is only a symptom and we are not sure that it is an enemy. Perhaps it is a friend."[4] Although this amicable relationship with fever certainly is true for those afflicted with neurosyphilis, not many pediatricians would agree with this tolerant view when their patient lies ill, "toxic" and, perhaps, convulsing. Most view fever as involving an increased expenditure of insensible and/or sensible water, but it must be remembered that fever is a reflection not only of increased heat production, but also, on occasion, decreased heat elimination. The factors involved in both these mechanisms are discussed below.

Heat Production. Rubner, in 1883, first established the fact that the heat produced by a person at rest is directly proportional to the surface area of his body.[40] It thus follows that the smaller the person the greater must his heat production be per unit of body weight. Surface area bears a rough quantitative relationship not only to heat production, but also to cardiac output, plasma volume, glomerular filtration rate, blood pressure, visceral organ size, oxygen requirement and nitrogen requirement.[43] Basal metabolic rate is low in early infancy, rises rapidly during the first few months of life and then subsequently falls slowly.[34] The requirements for growth and the relatively large surface area as compared to adults are the major determinants for food intake in the young, rapidly growing child. As a consequence, there is greater relative heat production calculated in terms of weight as compared to the adult.

Energy expenditure (caloric requirements) may be calculated by several simple systems, including the following:

(1) Caloric requirement = (100 − 3 × age in years) Cal./kg.[43]

(2) Caloric requirement for 0 to 10 kg. is 100 Calories per kilogram; for 10 to 20 kg., 1000 Calories plus 50 Calories per kilogram for each kilogram over 10; for 20 kg. and up, 1500 Calories plus 20 Calories per kilogram for each kilogram over 20.*[19]

Van't Hoff's law implies that the velocities of chemical reactions are increased two to three times per temperature rise of 10° C. It follows that in the febrile response to infectious disease, basal metabolism is accordingly elevated with resultant increase in heat production. Infections with high, persistent fever are accompanied by an increase of approximately 13 per cent of basal heat production for each degree C. rise in body temperature. The restlessness and hyperactivity common in febrile children increase heat production even further.[4] Protein destruction is common to all infectious processes, with urinary nitrogen elimination increased twofold or more. Chronic infections, however, do not induce this extravagant protein wastage. During convalescence from pneumonia the basal metabolic rate (and thus amount of heat production) may sink to low levels, possibly reflecting undernutrition and its effect on caloric expenditure.†[34]

Heat Elimination. In the process of heat elimination the febrile response of acute infections has an important bearing on fluid and electrolyte therapy. This involves the separate, although intimately related, homeostatic mechanism of regulation of body temperature. It should be realized that the fluid losses that are consequences of increased heat production may not occur if the thermoregulatory apparatus is not intact, as in the example of rare hypothalamic lesions producing hyperpyrexia.

Normal pathways of heat elimination are via the respiratory tract, by the warming of inspired air and evaporation of water, and by the skin. The skin eliminates heat by radiation (60 to 75 per cent of normal heat loss), conduction, convection, insensible water loss (25 per cent of normal heat loss) and sweating.[35] Multiple factors may affect the ability of both the respiratory tract and the skin to eliminate heat. The

* Confusion exists throughout medical literature over the use of the term "calorie." The unit used in human metabolism is the Calorie (kilocalorie), defined as the quantity of heat required to change the temperature of one kilogram of water from 14.5 to 15.5° C. Clarity of expression would be best served if the term "kilocalorie" were used to replace "Calorie."

† Undernutrition as the explanation of the lowered heat production during convalescence from pneumonia may be an oversimplification. Infants and children with pneumococcal pneumonia classically show a distinct hypothermia the second day of treatment. This could hardly be due to inanition, since it is specific for this particular infection.

amount of water loss and heat elimination via the respiratory tract is related to the temperature and water content of inspired air and to the volume of air breathed. Increasing the temperature of the inspired air (the humidity remaining the same) decreases water loss. Whereas exhaled air is usually 88 per cent saturated at 33° C., with hyperpnea the magnitude of water loss through the lungs may be up to 5 times normal.[10] Under conditions in which hyperpnea results for reasons unrelated to heat elimination, as in severe metabolic acidosis, the loss of water from the skin is reduced. Similarly, under conditions in which heat elimination from the skin is impaired, that from the respiratory tract is increased. When ventilation is reduced, although tachypnea is present, as in pneumonia, heat elimination (water loss) is not as great via the respiratory tract as when true hyperpnea is present. The loss of water and thus heat from the skin is likewise affected by multiple factors. Such factors as decreased skin circulation, warm external environment, clothing, absence of air movement or current around the subject all reduce the ability of the organism to lose heat by physical means. Skin acts as if it were a black body with a temperature of approximately 33.3° C. (92° F.); thus the body gains heat from the surrounding air and objects that are above this temperature, and loses heat to objects below this temperature.[10]

Newburgh et al.[31] found that an average of 25 per cent of total heat eliminated was done so by vaporization of water. Essentially the same percentage is removed at all levels of heat production in adults; thus heat production may be predicted from the insensible loss of weight. If it requires 0.58 Calorie to evaporate 1 gm. of water, it can be derived that insensible water losses approximate 45 cc. per 100 Calories of energy expenditure. This is usually divided into 15 cc. for pulmonary losses and 30 cc. for skin losses (exclusive of sweat), varying according to the factors listed above, for normal maintenance requirements. Calculated differently, Gamble[13] notes the average insensible loss of water in children to be 1.0 gm. per kilogram per hour.

The role of insensible water loss as a means of heat elimination is more variable in children than adults. When adults increase their activity, the percentage of total heat expenditure dissipated by means of insensible water loss remains essentially the same, i.e., 25 per cent. Children, however, during periods of increased activity, may show insensible losses extending to 90 ml. per 100 Calories, approximating 50 per cent of total energy expenditure.[19]

When heat production exceeds the losses produced by evaporation of the insensible water and by heat loss through radiation, conduction and convection, sweat is produced in amounts necessary to maintain normal body temperature. The efficiency of evaporation of sweat is not seriously hampered until the external humidity is greater than 80 per cent.

Air currents accelerate the rate of evaporation and thus the exchange of heat with the environment.[10] The importance of sweat, from a practical standpoint, in relation to fluid therapy, depends not only on estimations of observed quantities in any given patient, but also on an estimation of the effectiveness of the other routes of heat elimination. Darrow and Pratt[10] note, for example, that the calculated fluid losses in sweat in children with diarrhea in Texas averaged 70 ml. per kilogram per day. Although insensible water contains virtually no electrolytes, the electrolyte content of sweat is appreciable. The concentration of sodium and chloride in the sweat of normal babies approximates one fifth to one tenth of the values for unacclimatized adults. There was an average of 4.8 mEq. per liter of sodium and 5.8 mEq. per liter of potassium, and a sodium-potassium ratio less than 1, as determined on a small series of infants exposed to heat stress.[7] Older children have sweat electrolyte levels more closely resembling those of the adult when the sodium-potassium ratio approximates 4:1. On exposing infants to an environmental temperature of 91° F., Cooke et al.[7] demonstrated a threefold to fivefold increase in excretion of electrolytes by way of the skin with the onset of active sweating. Sweat volume approximated 45 to 65 cc. per kilogram of body weight per day under these circumstances.

In states of adrenal insufficiency the sweat glands are unable to elaborate a secretion of salt as hypotonic as that for normal persons. High sweat electrolyte levels were used by Conn[4] as a means of demonstrating disturbed adrenal cortical function before the advent of specific measurement of corticosteroid levels in plasma and urine. Similarly, the high sweat electrolyte levels in patients with mucoviscidosis explain the development of acute prostration and salt depletion on exposure of such patients to heat stress.

Although the demonstration of increased fluid and electrolyte loss through sweating is clear when children are exposed to heat stress, does the febrile response to infections initiate similar losses? If one divides the febrile response to infection into three phases, that of rising temperature (chill), steady pyrexia (fastigium) and falling temperature (defervescence), different relations between heat production and heat elimination are found.[35] As exemplified by malaria or the injection of pyrogen, the initial phase of rising temperature is characterized by increased heat production combined with decreased heat elimination, noted clinically by constriction of cutaneous vessels, and shivering. During the fastigium, most easily studied in pneumonia or typhoid fever, both heat production and heat elimination are increased. It is during this phase that DuBois made his calculations suggesting that heat production in fever averaged about 13 per cent of basal per 1° C. rise in body temperature. In the defervescent stage, as seen most strik-

ingly in the sweating stage of the malarial attack, the fall in temperature is due to mobilization of all the mechanisms that increase heat loss. Administration of calcium salts can abolish the chill reaction induced by pyrogens. Subsequent injection of endotoxin, however, produces a usual febrile response, indicating the predominant role of vasoconstriction and decreased heat loss in the pyrogenic reaction.[1]

To summarize briefly, the febrile response to infection involves an increased loss of hypotonic fluid subsequent to the homeostatic processes of temperature regulation. To draw up extremely specific recommendations for fluid therapy depending on the degree of febrile response would not seem desirable. Blood volume is increased in febrile states, suggesting that some caution should be directed towards the dangers of circulatory overloading. A constant relationship between heat production and heat elimination need not exist in the febrile state, except, perhaps, in the phase of steady fever. In addition, the other factors aiding in heat elimination may appreciably alter fluid requirements, depending on their relative effectiveness. Except in cases of adrenal insufficiency or mucoviscidosis, water balance alone is of major importance, electrolytes assuming a minor role. It should be remembered that dehydration, by itself, may produce a febrile response.

Cause of Fever in Infections. A thorough review of the recent advances in this field is beyond the scope of this article; the reader is referred to the discussions by Pickering,[35] Bennett and Cluff[1] and Wood,[45] from whom the following brief summary is taken. Although only partial mechanisms explaining the cause of fever in infections have been established, the beginning unraveling of the molecular mechanisms involved in its causation represents an extremely exciting investigative trend. Many bacteria, especially gram-negative bacilli and excluding most gram-positive cocci, have potent endotoxins which produce fever upon intravenous injection. These pyrogens, most of which are high-molecular weight polysaccharides or lipopolysaccharides, are not dialysable, and are relatively heat stable. Upon injection of a bacterial pyrogen, fever does not begin immediately, but only after a latent period of 15 minutes in the rabbit and 50 minutes in man. Upon repeated injection, a state of tolerance is induced, in which both the febrile and leukocytic responses are depressed but not abolished. This apparently does not reflect the development of specific antibodies, since there is cessation of tolerance after a two week interval following discontinuance of the injections. Furthermore, tolerance can be produced in patients with agammaglobulinemia and can be obliterated by agents such as Thorotrast that block the reticuloendothelial system.

The pyrogenic reaction to bacterial endotoxin seems to bear no relation to the virulence or pathogenicity of the organism from which it is derived. This dissociation between fever and the clinical severity of

an infectious process is common pediatric experience. The delay in onset of fever after injection of endotoxin plus the occurrence of fever in the absence of bacterial infection stimulated the search for endogenously produced pyrogens. When pyrogenic bacterial endotoxin is injected intravenously, the endotoxin itself is rapidly cleared from the blood and is replaced by a circulating pyrogen indistinguishable from that which can be extracted from polymorphonuclear leukocytes. This endogenous pyrogen is similarly found after intravenous injection of influenza virus, in the febrile phase of experimental pneumococcal peritonitis and in streptococcal peritonitis.

Unlike the bacterial endotoxins, endogenous pyrogen is inactivated by heat, manifests a short latent period, produces slight or no post-injection leukopenia and produces no tolerance on repeated injection. It thus appears that, with bacterial pyrogens, the endotoxin-induced fever "results from the dual action of two pyrogenic substances: the endotoxin itself, which acts upon the leukocytes (and possibly other cells), causing them to release endogenous pyrogen; and the resulting endogenous pyrogen, which in turn acts upon the thermoregulatory centers of the brain."[45] How general this phenomenon of endogenous pyrogen formation is in the many varied states in which fever occurs remains to be determined. That it plays an extremely important role in the febrile response of acute infectious processes seems fairly definite.

Morphologic changes in the adrenal gland may be produced by bacterial pyrogens (and may be found during the course of acute infections clinically), but there is no evidence supporting the concept that the effects of bacterial pyrogens are *directly* mediated by the pituitary-adrenal axis. However, several recent experimental findings indirectly relating the adrenal cortex to the bacterial pyrogenic reaction are interesting enough to justify inclusion here.

It has been shown that the adrenal cortex concentrates radioactive carbon (C^{14}) after the injection of C^{14}-labeled polysaccharide complexes from *Klebsiella pneumoniae*. The C^{14} material remains in the adrenal cortex for several months. Some of the C^{14} label is present in substances retaining the immunologic properties of the original polysaccharide. Cortisone selectively inhibits this adrenal C^{14} uptake, pointing to a possible relationship with steroidogenesis. Jones et al.[21] produced a transient but definite rise in plasma 17-hydroxycorticosteroids (17-OHCS) in guinea pigs after intravenous injection of this haptenic, nonlethal complex. It was shown that plasma 17-OHCS fell to normal levels while abundant polysaccharides were still circulating in the blood stream. Subsequent studies revealed a "neutralization" of this adrenal-activating ability when the polysaccharide complex was exposed to blood plasma in vivo or in vitro, suggesting that further investigation of endogenous pyrogen and its effect on the adrenal might be fruitful.[22]

In another area of investigation, recent studies have revealed the existence of an endogenously elaborated adrenocortical steroid which produces fever. Migeon and Plager[28] had found the most prominent 17-ketosteroids of peripheral, adult human plasma to be dehydroepian-

drosterone and androsterone. No etiocholanolone was noted in normal, adult plasma, even though this steroid has been found in large quantities in urine. Kappas et al.[23] injected recrystallized etiocholanolone into normal adults and produced an acute pyrogenic and inflammatory reaction. Subsequently Bondy et al.[2] reported the cases of two men with periodic fever who were found to have unconjugated etiocholanolone in their plasma. In one case no etiocholanolone could be detected in plasma between attacks. Gardner and Migeon[16] measured the 17-ketosteroids in the plasma of a boy with congenital adrenal hyperplasia and

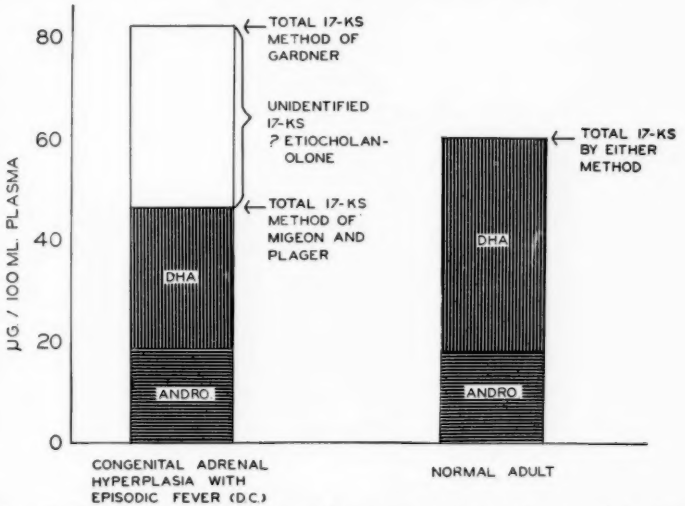

Fig. 27. Unusual plasma 17-ketosteroid pattern in a boy with congenital adrenal hyperplasia and periodic fever. (From L. I. Gardner and C. J. Migeon: Unusual Plasma 17-Ketosteroid Pattern in a Boy with Congenital Adrenal Hyperplasia and Episodic Fever. *J. Clin. Endocrinol. & Metab.*, Vol. 19. Courtesy of Charles C Thomas, Publisher.)

periodic fever. They found considerable amounts of an unidentified 17-ketosteroid which was neither dehydroepiandrosterone nor androsterone. In light of the findings of Bondy et al.[2] it is likely that this 17-ketosteroid was in fact etiocholanolone. Figure 27 shows graphically the unusual plasma 17-ketosteroid pattern in the boy with congenital adrenal hyperplasia and periodic fever studied by Gardner and Migeon.[16] Thus the finding that the human adrenal cortex can produce a pyrogenic steroid adds new dimensions to the relationship between the adrenal cortex and fever.

General Clinical Features

Although infections induce a multitude of clinical features that are commonly seen in the reaction pattern of children, only the effects of

infection on intake and on the production of convulsions are chosen because of their important relations to fluid and electrolyte therapy.

ABERRATIONS OF INTAKE. Children with infections show interference with normal intake more commonly than do adults. The implications of decreased intake are also far more serious in children, owing to their greater obligatory turnover of fluid. Thus, even if the problems of deficit therapy in infection may be difficult to quantitate and may require an analysis of numerous factors, as has been discussed, the provision of normal maintenance requirements must be ensured in sick children. If, then, careful history-taking reveals the commonly found anorexia and/or vomiting coincident with infection, parenteral provision of maintenance requirements must be provided, as outlined in other clinics in this volume.

CONVULSIONS. Acute, febrile infections are the most common causes of convulsions in children between the ages of one month and four years. Although dehydration should be corrected in such children, it has long been recognized that overhydration may precipitate convulsions in those children with convulsive tendencies. Accordingly, caution should be taken to avoid supplying fluid and electrolyte in excess amounts during the period of convulsions and in the postictal phase. Means should be taken to increase heat elimination by physical means, such as increasing air currents or decreasing environmental temperature, and by the use of antipyretic agents. In addition, one need only mention the danger inherent in producing too rapid a fall of body temperature by physical means.

SPECIFIC FACTORS IN INFECTIONS

Implications of Metabolic Transfer across Cell Membranes

"All living cells are faced by two problems which are clearly antagonistic: They must retain their integrity, constraining their component molecules within a definite space, but, on the other hand, require a continuous or periodic interchange of numerous substances with their surroundings."[42] The exchange of water and electrolyte between intracellular and extracellular spaces depends on metabolic processes as well as such physical properties as differences in concentration, differences in activity coefficients, differences in electrical potential between phases in contact with a membrane and solvent drag force arising from the passage of solvent through the membrane.[8, 42] Although the specific mechanisms remain to be definitely identified, there is little doubt that the transport of sodium across the cell membrane is an active mechanism (involving energy expenditure).[6] Any mechanism, then, that interferes with this energy-consuming transport will allow intracellular accumulation of sodium at the expense of potassium.

Notable alterations of cell membrane permeability have been reported in the following febrile states: lymphangitis, bacteremias, Rocky Mountain spotted fever, artificial fever and malaria.[33] In studying the malarious monkey, Overman[32] found little alteration of plasma levels of Na^+, K^+ and Cl^- during the course of fatal *Plasmodium knowlesi* infections. The Na^+ content of erythrocytes (nonparasitized) increased about 100 per cent before death, with corresponding decreased K^+ levels. It is in tuberculosis, however, that the most intensive and revealing studies have been performed. In pulmonary tuberculosis asymptomatic hyponatremia and hypochloremia have been consistently found, not correlated with either HCO^{3-} or pH values of serum.[26, 39] In their study of 16 patients with tuberculous meningitis Harrison et al.[18] found a consistent pattern of electrolyte alteration as follows: (1) in extracellular fluid, hyponatremia and hypochloremia with no consistent changes of potassium; (2) in erythrocytes, elevation of sodium levels with no consistent change in potassium; and (3) in muscle cells, both an elevation of sodium and depression of potassium levels. Potassium therapy did not correct the electrolyte abnormality in their patients. Cheek[3] has subsequently confirmed these findings, although he recommends daily administration of 40 to 80 mEq. of K^+ per square meter of body surface during the presence of the altered electrolyte pattern. It thus appears likely that certain infectious processes inhibiting cellular mechanisms necessary for maintenance of electrolyte equilibrium may produce a sodium-potassium transfer between intracellular and extracellular spaces.

Relation between Nutrition and Infection

The implications of metabolic transport across cell membranes discussed above take on added meaning when the complication of malnutrition is superimposed. In studies of malnourished children Frenk et al.[12] have documented a pattern of body composition resembling to a considerable degree that found in tuberculosis. In most cases muscle and skin show an increase in total water, sodium and chloride content. When malnutrition progresses to the stage of edema formation, intracellular potassium concentration is depressed. When malnourished patients are exposed to the stress of surgery (and presumably also infection), an accentuation of this sodium-potassium shift occurs in addition to the usual dilutional hypotonicity and mobilization of cell potassium that accompanies the stress response in well nourished persons.[29] Repair of this state depends on correction of the chronic energy deficit by protein and caloric supplementation. Excessive water intake only accentuates the situation.

Cardiovascular Collapse

During the course of meningococcemia or other infections, especially in the very young, the development of petechiae and vascular collapse remains an all too common enigma facing the clinician. In such states therapy consists in administration of blood or plasma in order to establish an adequate circulating blood volume. The use of antibiotics, adrenocortical steroids and/or pressor amines in such situations is discussed elsewhere in this volume.

SUMMARY

1. Infections most commonly induce aberrations of fluid and electrolyte balance when productive of excessive losses, as in diarrhea, when involving the central nervous system or when associated with limitations placed on normal homeostatic mechanisms, as in renal or pulmonary infections.

2. Common to most infections are fever and the metabolic reaction to stress. Multiple forms of stress, including infection, produce a relatively general metabolic pattern, characterized by dilutional hypotonicity, expansion of blood volume, fall in serum Na^+ and relative increase in serum K^+ (Na^+ shift from extracellular to intracellular space) and negative nitrogen balance. Qualitative as well as quantitative differences in the fluid and electrolyte pattern following varying forms of stress have been defined.

3. Fever in infections represents a resultant of two forces, heat production and heat elimination. Only in the presence of persistent, sustained hyperpyrexia can the generalization be made that basal heat production increases approximately 13 per cent for each degree C. rise in body temperature. Usually, if the increased heat production in infectious diseases can be met by physical means of heat elimination, including insensible water loss, the need is for water alone, in addition to maintenance requirements. If, however, sweating occurs, appreciable losses of electrolyte as well as water occur and must be replaced. The occurrence of fever does not necessarily indicate that fluid losses can be assumed. An evaluation of the various factors involved in heat elimination in any given patient must be made in order to assess fluid and electrolyte needs.

4. Clinically, the occurrence of anorexia and/or vomiting is extremely common during the course of infections in infants and children. If such are present, maintenance needs, in addition to replenishing excessive loss of fluid and electrolyte, must be provided by parenteral means.

5. The exchange of water and electrolyte between intracellular and extracellular spaces depends on the expenditure of energy. That sodium transport involves energy expenditure is a confirmed fact, although the

exact mechanism remains unclarified. Any process that interferes with the expenditure of energy in cellular processes may produce a sodium-potassium shift with intracellular sodium accumulation and potassium depletion. It should be noted that states of malnutrition also present grossly similar alterations of body composition.

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766 Irving Avenue
Syracuse 10, New York

FLUID THERAPY IN SURGICAL CONDITIONS

ELEANOR COLLE, M.D.

ELSA PROEHL PAULSEN, M.D.

The plan for parenteral alimentation of the pediatric surgical patient, like that for the adult surgical patient, may be conveniently divided into three phases: preoperative, operative, and postoperative. The aim of the first is to correct, so far as possible, existing deficits of water and electrolytes and disturbances of acid-base balance which have occurred because of the process for which surgery is contemplated; the purpose of the last two is to maintain this balance during a period when natural alimentation is impossible. In any given instance one phase may be more important than the others. A child with pyloric obstruction may enter the hospital with moderate dehydration and hypochloremic alkalosis. In such a patient preoperative correction is of great importance, but after a successful surgical attack the early institution of oral feedings will usually result in a relatively easy and uneventful postoperative course. On the other hand, a child undergoing operation for a traumatic abdominal condition may be in good nutritional and fluid balance at the time of the accident, so that preoperative preparation is unimportant, but control of shock during operation and the persistence of ileus postoperatively may lead to a prolonged period when parenteral alimentation is necessary.

The cornerstone of therapy in each phase must be the provision of maintenance requirements for fluid, calories and essential minerals. To these maintenance requirements are added the specific demands imposed by disease, abnormal losses and the peculiar metabolic alterations which follow the operative intervention. Variation in activity, the presence of fever, increased respirations, and fluctuations in environmental temperature and humidity will all modify these requirements.

In the care of surgical patients pre-existing deficits and continuing losses are added to the maintenance requirement. The former are estimated by the degree of dehydration present and are conveniently expressed as a percentage of the body mass. The latter are ideally reckoned from actual measurements of losses as they occur.

Consideration of the foregoing makes it obvious that no rule of thumb can be devised to apply to all pediatric surgical patients. Each

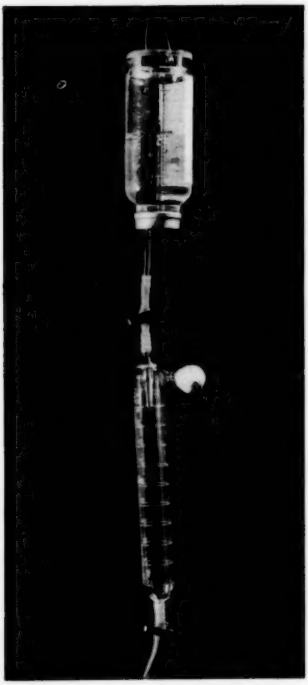

Fig. 28. Buret flask designed for delivery of small amounts of fluid.

patient must be assessed and reassessed as an individual problem. In order to evaluate the patient, an adequate chart record must be maintained. An accurate weight preoperatively is imperative as a basis for estimation of all needs, and daily weights are of value in detecting small changes in underhydration and overhydration. Losses which are readily measurable, the urine output and the volume of fluid removed by intubation, must be accurately charted. If the problem at hand is a complicated one, these measurements should be made every few hours so that replacement can keep pace with loss. In the measurement of gastrointestinal losses a record of the amount and kind of solution

used for irrigation of tubes must also be kept. If this is not done, the volume of fluids lost from the gastrointestinal tract may be overestimated and, accordingly, over-replaced. Since replacement of these losses is usually made with solutions relatively high in electrolytes, such overestimation may lead to excess administration of sodium and chloride. This is, of course, most important in the care of the very young child, in whom the volume of the irrigating fluids may be close to that of the total volume of intestinal fluids being withdrawn.

It is essential that fluids and electrolytes for any given time be administered evenly over that period. Accurate delivery of small amounts is facilitated when a calibrated 100-ml. buret is fed by the bottle containing the electrolyte solution (Fig. 28). The amount of fluid to be administered over a three- or four-hour period can be introduced from the original bottle into the buret and the tubing from bottle to buret then clamped. If the rate of infusion is now inadvertently increased, it is impossible for more than a three- or four-hour load to be administered during any short period. If such an accident does occur, infusion can be slowed down or stopped for a time and then restarted.

PREOPERATIVE PARENTERAL FLUID THERAPY

Elective Surgery

The problem of operating upon the chronically malnourished patient so often encountered in adult surgery is rarely seen in pediatric practice. When it does exist, appropriate methods to increase caloric intake by oral means should be initiated when feasible.

In the majority of elective surgical procedures the patient is in good fluid and electrolyte balance on the day of operation, and the problem of replacing pre-existing deficits does not exist. If, however, routine preoperative schedules adopted for adults are adhered to for younger patients, significant dehydration may occur. This danger is greater in the younger child. Withholding all fluids should not be continued for more than four to six hours before operation. If longer periods of fasting are required by the surgeon or anesthesiologist, an infusion of an appropriate hypotonic electrolyte and glucose solution should be started, and maintenance requirements of fluids should be administered evenly over the period in question.

When emergency surgery is to be done, the problem of replacing severe deficits which have occurred as the result of vomiting (pyloric stenosis, intestinal obstruction) or diarrhea (ulcerative colitis) during a fairly short period may be encountered. The most common problem is that of the patient with vomiting who has a hypochloremic alkalosis by virtue of loss of hydrogen and chloride ions in gastric contents, exchange of hydrogen ion for cellular potassium ion and subsequent

urinary loss of potassium. Significant dehydration is almost invariably present. Regardless of the apparent gravity of the surgical situation, an attempt to improve fluid and electrolyte balance before operation is advisable. If shock or impending circulatory collapse is present, the use of blood or plasma is indicated. After this, hydration of such a patient should be initiated with a hypotonic saline solution (approximately one-third normal saline in 5 per cent glucose; this contains 52 mEq. per liter each of sodium and chloride). Once adequacy of kidney function is indicated by an adequate flow of normal urine, a multiple electrolyte solution, hypotonic to plasma (40 mEq. per liter of sodium, 35 mEq. of potassium, and 40 mEq. of chloride), is started. If the alkalosis is severe, the solution is often supplemented with added potassium either as the acetate or the chloride salt so that the total potassium intake is between 100 and 150 mEq. per square meter per 24 hours (3 to 4 mEq. of potassium per kilogram per 24 hours). It is convenient to remember in this regard that 1 ml. of a 10 per cent solution of potassium chloride contains 1.3 mEq. of potassium ion. The total amount of fluid to be administered is determined by adding to the maintenance requirements sufficient fluid and electrolyte to make up the estimated deficits within a 24- to 36-hour period. If gastric losses continue after curtailment of oral intake, these are measured and replaced with a solution of appropriate composition. The exact time when any given patient is ready for operation is a matter of clinical judgment. A representative case history may illustrate this point.

Case I. A month-old infant was admitted with a 1-week history of projectile vomiting, diminished stooling and failure to gain. A pyloric tumor was felt in the right upper quadrant. The infant weighed 3220 gm.; his weight 2 weeks previously had been 3400 gm. The surface area was 0.22 square meter. Routine blood work was normal.

		INTAKE			SERUM			
Time hr.	Vol. ml.	Na^+ mEq.	K^+ mEq.	Cl^- mEq.	Na^+ mEq./L.	K^+ mEq./L.	Cl^- mEq./L.	HCO_3^- mEq./L.
0					137	3.8	77	42
0–12	250	11	–	11				
12					131	3.1	70	43
12–24	335	16	9	23				
24					135	—	87	35
24–36	310	15	8	23				
36					137	4.6	96	30

The infant was operated upon 36 hours after admission. The postoperative course was uneventful, and oral feedings were started 12 hours after operation.

The maintenance requirements for this infant were estimated to be between 300 and 350 ml. (1500 ml. per square meter per 24 hours) in a 24-hour period. The deficit was estimated to be between 200 and 250 ml. Accordingly during each of the 12-hour periods he was given 150 ml. of fluid (maintenance) plus 100 to 150 ml. of fluid (for gradual repair of existing deficit). Maintenance requirements for sodium, potassium and chloride were estimated as 1 to 2 mEq. per kilogram per 24 hours (5 to 10

mEq. per square meter per 24 hours). Deficits of sodium and potassium were estimated to be 10 to 15 mEq. per kilogram and for chloride 15 to 20 mEq. per kilogram. During the 36 hours of therapy about three fourths of the deficits of sodium and chloride were administered and about half of the potassium deficit. Although hydration was improved at the end of the first 12 hours of therapy, there was no correction of the hypochloremic alkalosis until potassium-containing solutions were administered. The amount of potassium administered was at the upper limits of the amounts it is desirable to give in a 24-hour period. More ideally, repair could have been achieved had potassium-containing solution been started earlier and the same total amount of potassium administered more evenly over the 36-hour period. Although the concentration of electrolytes in the serum was not "normal" at 36 hours, substantial correction had been achieved, hydration was good, and operation was well tolerated. It was felt that any further postponement of operation would have added nothing more than an additional period of starvation. Postoperatively, maintenance fluids only were given, oral feedings were initiated 12 hours after operation, and recovery was uneventful.

If the pre-existing cause of dehydration had been predominantly from the lower gastrointestinal tract (diarrhea), deficits of sodium and potassium losses would have been proportionately greater than those of chloride.

If peritonitis is present, considerable local accumulation of fluid may have taken place. This source of fluid loss, not readily apparent from the history, must be taken into account in planning a rehydration program.

In the newborn period, operation is usually performed only on an emergency basis. However, the anomalies requiring surgical correction in this period (obstructing lesions of the gastrointestinal tract) usually manifest themselves dramatically within the first day or two of life. Since the normal infant during this period may take in little or nothing in calories or fluids, the problem of repair of deficits is much less unless vomiting has taken place; the latter is encountered most often in obstructions of the lower intestinal tract. When the infant appears clinically dehydrated, fluids should be estimated according to the severity of the dehydration. To this are added maintenance requirements. In the young infant these may be considered approximate to what the normal newborn is taking during this period: day 1, nothing by mouth, days 2 and 3, 50 cc. per kilogram, and thereafter amounts closely approximating those given to older infants. Because of the limitations in the ability of the very young infant to form a urine with maximal concentration, it is wise to use a solution in which the ratio of solutes to water is considerably lower than in the solution used for parenteral alimentation of the older patient (sodium, 25 mEq. per liter; chloride, 22 mEq.; and potassium, 20 mEq.). Young infants are slow to excrete a water load. For this reason intravenous fluids should be given evenly over the 24-hour period, and special apparatus which prevents the sudden administration of large volumes of fluid should be used.

OPERATIVE PERIOD PARENTERAL FLUID THERAPY

Although the operative period itself may be of relatively short duration, losses of fluid may be substantial. This is particularly true again for the younger children, whose surface area is correspondingly larger. Most of the increased losses will be insensible and hence are essentially losses of water free of electrolytes and should be replaced as such.

During the actual operative period, control of the parenteral fluid intake is usually in the hands of the anesthesiologist. It is our practice to discontinue use of electrolyte-containing solutions during this period, substituting instead either a 5 per cent glucose solution or one-fifth to one-third normal saline in 5 per cent glucose. Potassium- and phosphate-containing solutions, especially, should be avoided, since concentrations of these ions may rise rapidly in the serum if shock and temporary anuria intervene. In addition, we find that the use of the buret type of fluid container is of great value in the prevention of unintentional fluid loads in the operating room. The amount of fluid estimated for the operative time is allowed into the buret at the time the child leaves the children's ward. It is then less likely that he will receive more than that amount of fluid. The change to more adequate multiple electrolyte solutions to meet the specific needs of the patient is made after operation as soon as adequacy of renal function is again demonstrated.

POSTOPERATIVE PARENTERAL FLUID THERAPY

The fluid regimen for the postoperative period depends upon the duration and severity of the surgical procedure and upon the nature of the continuing losses which may have been imposed by the procedure. Any fluid program for a given 24-hour period should be re-evaluated several times during that period, and changes in the weight, urine output and determination of serum electrolytes should be a guide to changes in the fluid program. Rigid adherence to any one plan cannot be relied upon to produce uniformly successful results.

Certain conditions which accompany a surgical procedure should be pointed out:

1. A transient period of antidiuresis will usually follow the immediate postoperative period in older children and adults. This is potentiated by certain drugs (morphine) and anesthetic agents (ether). A period of antidiuresis, in our experience, is generally absent in young infants.

2. A period during which sodium is retained may occur with the period of antidiuresis. Again, in our experience, this has been a more frequent occurrence in older children and adults.

3. The combination of antidiuresis and sodium retention may lead to excessive accumulation of water with expansion of the extracellular

space and a dilutional hyponatremia if administration of fluid and salts is excessive.

4. Increased excretion of nitrogen and potassium is almost always encountered postsurgically, and the magnitude of the negative potassium balances so developed may aggravate an existing metabolic alkalosis.

These changes are less marked the shorter the surgical procedure. Therefore the regimen for parenteral alimentation planned for a young child undergoing an elective herniorrhaphy with no excessive extrarenal losses will be vastly different from that planned for a child having a ruptured appendix.

In the former the need is for short-term provision of maintenance requirements of water, electrolytes and calories and can be met by infusion of approximately 1500 ml. per square meter of a multiple electrolyte solution containing between 25 and 40 mEq. per liter of sodium, 20 to 35 mEq. of chloride and moderate amounts of potassium, viz., 20 to 30 mEq.

In the latter the presence of fever will increase insensible losses, thus augmenting the child's maintenance requirements. In addition, the postoperative course will be complicated by continuing infection and ileus with significant extrarenal loss of fluid and electrolytes. The composition of gastric content varies, but the sodium concentration will usually range from 40 to 80 mEq. per liter, that of chloride from 90 to 140 mEq., and potassium 5 to 10 mEq. The total fluid requirements would consist of the maintenance requirements plus the amount removed by gastric suction—the latter to be replaced by a solution *similar in composition* to gastric content. On the first postoperative day the urine output and specific gravity will indicate the extent of the antidiuresis, and allowances for maintenance requirements of both sodium and water may be reduced proportionately. Suction losses should be checked at six- to eight-hour intervals and such losses promptly added to the day's fluid requirements. If significant ileus is present, a gastric tube may be withdrawing fluid from the upper small bowel. If there is doubt as to the composition of the fluid, analysis of an aliquot is advisable.

For the occasional patient with an ileostomy, adequate care becomes more difficult. Losses are more difficult to estimate, although weighing of dressings may yield valuable information. The composition of sodium in a recent ileostomy may be twice as high as that in gastric juice, and the replacing solution should be accordingly higher in sodium (Table 21).

In patients in whom the surgical stress has been severe or in whom infection is still present, large urinary potassium losses may be present. The development of a hypochloremic alkalosis (low serum chloride, high serum pH and high serum bicarbonate) should suggest this pos-

TABLE 21. *Sodium, Chloride and Potassium Content of Gastric Juice in Ileostomy Patients*

TYPE OF FLUID	SODIUM	CHLORIDE	POTASSIUM	AUTHOR
	Milliequivalents per Liter			
Nasogastric decompression	46	72	7	Lowe[12]
Ileostomy, recent (adult)	130	115	11	Lowe[12]
Ileostomy, recent (child)	134	81	14	Lowe[12]
Gastric juice	20–80	100–150	5–20	Cooke[4]
Small bowel	100–150	90–130	5–15	Cooke[4]
"Duodenal drainage"	20–133	40–150	3–20	Lowe[13]
Nasogastric decompression (average 20 determinations) in newborns	70	85		Colle[3]

sibility. Determination of potassium content in the urine in the postoperative period is valuable in estimating replacement needs. Despite the presence of a low serum chloride and a somewhat low serum sodium, correction of the electrolyte imbalance with sodium chloride solutions alone can rarely be achieved. The following case emphasizes some of these points.

CASE II. An 8-year-old girl was operated upon for repair of a patent ductus. Her preoperative weight was 24.3 kg., her surface area estimated at 0.8 square meter. On the day of operation she was given parenteral fluids for 12 hours before operation.

PERIOD	TIME HR.		AMOUNT CC.	Na	K	Cl	Na	K	Cl	Co_2
				mEq.			mEq./liter			
I	12–0	In.	—	—	—	—	137	4.4	98	26
		Out.	567	53.5	19	57				
		Bal.	−567	−53.5	−19	−57				
II	0–12	In.	350	14	25	27	135	4.	—	28
		Out.	167	12	10	30				
		Bal.	+183	+ 2	+15	− 3				
III	12–36	In.	1150	46	40	46	135	4.2	—	28
		Out.	490	15	67	35				
		Bal.	+660	+31	−27	+11				
IV	36–60	In.	1290	51	58	64	—	3.1	87	30
		Out.	935	2	58	24 (urine)				
			675	23	9	54 (gastric)				
		Bal.	−320	+26	− 9	−14				
V	60–84	In.	1950	115	69	115	129	5.2	87	36
		Out.	1047	4	55	23 (urine)				
			411	14	5	32 (gastric)				
		Bal.	+493	+97	+ 9	+60				
VI	84–103	In.	1650	66	58	66	127	5.3	90	35
		Out.	1465	43	30	40				
		Bal.	+185	+23	+28	+26				
VII	108–132			Oral feedings started			135	4.7	94	30

It is of interest to note here the postoperative antidiuresis; the urine output for the second 12 hours of the day of operation was only about one fourth that for the first 12 hours before operation. There is a sodium retention (moderate) which persisted through the next day. During the fourth period gastric retention developed, and nasogastric suction was instituted. Urinary sodium excretion was further curtailed. The concentration of electrolytes in the serum remained relatively normal until the loss of gastric juice occurred. At this point a moderate degree of hypochloremic alkalosis developed which was corrected, not by administration of added sodium chloride, as was attempted during period V, but rather after a positive balance for potassium had been maintained for 2 days. Maintenance requirements for this child were estimated to be about 1200 to 1400 ml. per 24 hours. During the first 12 hours fluids were restricted because of the expected antidiuresis. During the second 24 hours maintenance requirements were administered, and there was still a positive water balance. Accompanying this was a positive balance of sodium. Urinary potassium losses were large. When the losses of chloride in excess of sodium occurred on the following day, the typical chemical picture of a hypochloremic alkalosis was manifest. During this period fluids were planned by giving maintenance requirements of 1200 ml. plus estimated gastric losses from the day before. The administration of extra sodium during period V was not indicated, since at no time had sodium losses been excessive. Return of the serum concentration of sodium to normal occurred only with repair of the potassium deficits.

Especially in patients who have had thoracic surgical procedures, it must be remembered that an elevated carbon dioxide content or a "carbon dioxide-combining power" may represent a primary respiratory acidosis due to carbon dioxide retention and not a metabolic alkalosis. Determination of arterial pH is necessary for differentiation. If the patient is in respiratory acidosis, attempts to improve ventilation are, of course, necessary when possible.

In the newborn infant the amounts of maintenance fluids are, as indicated above, lower during the first three to four days of life. Thereafter they approach those found for the older child. As indicated above, maintenance requirements for the newborn are usually supplied in the form of a solution with a lower ratio of solutes to water. However, continuing losses from nasogastric decompression or ileostomies must be replaced with solutions of appropriate electrolyte concentration and not with the more hypotonic solution. In our experience the development of a potassium-deficient, hypochloremic alkalosis is most uncommon in the infant who has an operation during the first four days of life. Hence supplementation with potassium above maintenance needs is probably not indicated and may be dangerous.

Two cases will illustrate the use of fluids in the postoperative period in the newborn.

CASE III. An infant was admitted to the hospital at 4 days of age with the history of having vomited each feeding. Mild dehydration was present on admission. Operation was performed after 10 hours of preparation. A partial duodenal obstruction was encountered. Weight on admission was 2430 gm., surface area estimated at 0.20 square meter.

TIME HR.		VOL. ML.	Na	K	Cl^-	Na	K	Cl^-	CO_2
				mEq./L.					
0						—	—	93	27
0–12	In.	180	6.1	1.6	5.7				
	Out.	30	1.9	1.1	0.1 (urine)				
		30	4.1	0.4	4.9 (gastric)				
	Bal.	120	0.1	0.1	0.7				
12–30	In.	213	5.3	4.3	5.1				
	Out.	93	1.8	2.8	0.2				
	Bal.	120	3.5	1.5	4.9				
30						140	5.0	111	26
30–54	In.	305	7.6	6.1	6.7				
	Out.	225	2.6	5.2	0.5 (urine)				
		45	4.2	0.3	5.0 (gastric)				
	Bal.	35	0.8	0.6	1.1				
54–78	In.	284	7.1	5.7	6.2				
	Out.	197	2.9	5.0	0.2 (urine)				
		45	4.2	0.3	4.9 (gastric)				
	Bal.	42	—	0.4	1.1				
78						140	4.2	93	24
78–102	In.	329	8.2	6.6	7.3				
	Out.	213	3.6	5.3	1.1				
	Bal.	116	4.6	1.3	6.2				
102–126	In.	216	4.3	5.3	4.0 (oral feedings)				
	Out.	178	3.9	4.5	1.4				
	Bal.	38	0.4	0.8	2.6				
126–150	In.	390	9.7	13.2	9.3				
	Out.	171	2.1	2.7	0.5	143	5.4	102	24
	Bal.	219	7.6	10.5	8.8				

Despite the fact that this infant had been vomiting for 3 days, he was only mildly dehydrated at the time of admission. His maintenance requirements for fluid were calculated to be about 300 ml. per 24 hours (1500 ml. per square meter per 24 hours). His maintenance requirements for electrolytes were approximately 2.5 to 5 mEq. per 24 hours of sodium, potassium and chloride. During the first 12 hours he was given half of his maintenance fluid requirements and some for repair of deficits. The deficit is difficult to estimate; but since this infant was only 4 days old, his maintenance requirements during the preceding period would have been low, and his main losses were vomitus. After operation the urine output was good, and gastric losses varied between 30 and 45 ml. per 24 hours. The amounts of sodium and chloride lost in gastric drainage each day were about 4.0 mEq. of sodium and 5.0 mEq. of chloride, and these were added to the estimated maintenance requirements.

Case IV. An infant was admitted at the age of 2 days with a tracheo-esophageal fistula. Because of pneumonitis, operation was not performed until 4 days of age. The infant weighed 3060 gm., with an estimated surface area of 0.20 square meter. Fluid therapy consisted of 200 ml. of fluid daily containing 2.5 mEq. of sodium, 2.0 mEq. of potassium and 2.2 mEq. of chloride. Urine volumes on this regimen were between 125 and 175 ml. daily. The concentration of electrolytes in the serum

was normal on the day of operation. On the third postoperative day the serum concentration of sodium was 151 mEq. per liter, of potassium 5.8 mEq. per liter, of chloride 108 mEq. per liter. With an increase in the total daily amount of fluids, the concentration of electrolytes in the serum gradually fell to normal.

Maintenance requirements for this child had been estimated to be about 300 ml. per 24 hours. Slightly less than this amount was given, since the infant was in a saturated mist atmosphere and because the surgeon wished the baby on the "dry side." Urine volumes remained good, and there was a slight elevation of concentration of electrolytes in the serum on this level of fluid intake. These returned to normal when the total amount of daily fluids was increased.

Neurosurgical Procedures

In our experience patients undergoing intracranial surgery have on occasion presented unusual postoperative complications.

Most distressing has been the development of a water retention which may persist for several days on an intake clearly not excessive. Urine volumes are usually small, specific gravities high. There is a dilutional hyponatremia which may lead to convulsions. The onset may be insidious. Such cases are probably related to those described by Nyhan and Cooke[17] and by McCrory.[16] The etiology is obscure, but they seem related to those situations experimentally produced by chronic administration of Pitressin (antidiuretic hormone). Prevention is simpler than treatment. For this reason we prefer to give somewhat less than maintenance water requirements (about 75 per cent) on the first day or two after operation. If the urine output is small, the specific gravity high, and, most important, if the difference between intake and output is greater than that which could reasonably be assumed to be insensible water loss, the amount of water should be even further restricted. Careful weights are of value in detecting early water retention before frank edema develops. Once the hyponatremia has become established, isotonic saline solution may be indicated, although, since sodium excretion may be already reduced, osmotic diuresis induced by urea or mannitol may be of more value. If the hyponatremia is asymptomatic, water restriction alone is effective.

The opposite defect, hyperelectrolytemia, may also occur. This is most commonly encountered in comatose postoperative patients who are maintained on tube feedings disproportionately high in solute (protein and electrolyte) and in whom the thirst mechanism is not operating because of impairment of consciousness. The simple provision of more water usually suffices to correct the defect.

Occasionally, after decompression operations drainage of cerebrospinal fluid may be an important source of loss of fluid. Care should be taken to check the dressings of such patients to detect any such loss.

SUMMARY

1. The needs of the surgical patient for fluid and electrolyte requirements are defined by the provision of maintenance requirements, replacement of previously incurred deficits and replacement of continuously occurring losses.

2. Accurate records of the patient's weight, fluid and electrolyte intake and output and frequent measurement of concentrations of serum electrolytes are a necessity for the individualization of such a program.

3. In young children, especially, daily fluid and electrolyte requirements must be administered over a 24-hour period. Special apparatus designed for the delivery of small amounts of fluid will help prevent unintentional water loads.

4. The surgical operation with its attendant anesthesia may be expected to produce in older children some degree of antidiuresis and sodium retention. In the younger infants and newborns this is rarely encountered.

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University of Minnesota Medical School
Minneapolis 14, Minnesota (Dr. Colle)

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FLUID THERAPY IN BURNS, TRAUMA AND SHOCK

CHARLES C. WOLFERTH, JR., M.D.

GERALD W. PESKIN, M.D.

BURNS

Successful treatment of burns remains a problem of major magnitude. Approximately 7000 deaths per annum occur from burns in the United States. A conservative estimate would be that approximately 70,000 burned patients are hospitalized every year. The cost of burns in terms of human suffering and loss of social usefulness is inestimable.

It is thought that at least half of all burn accidents could be prevented. Open fires and unprotected heating units are responsible for an unusually large number of burns, particularly in the southwestern section of the United States. Ignition of clothing is the frequent mode of burning, particularly in young girls, whose skirts are readily kindled by contact with fire. Bleck's[3] analysis of 344 burned children revealed that ignition of clothing caused the burn in 46 per cent. The home, rather than the place of employment, is the place where burns are most likely to occur. In Colebrook's[4] series, as well as in Moyer's,[9] 70 per cent of all burning accidents occurred around the home. Unfortunately, children are commonly the victims in burning accidents. Colebrook reported that 70 per cent of all burned patients admitted to his hospital were children, those under the age of five being most often affected. In the United States the proportion of burned children is somewhat smaller, perhaps 30 to 50 per cent.

The burn wound evokes a systemic response reflected as a myriad

From the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, and the Hospital of the University of Pennsylvania, Philadelphia.

of pathophysiologic processes. Proper care of the burned patient requires the integration of many aspects of therapy such as fluid balance, wound management, anesthesia, surgical technique, nutrition, treatment of infection, physiotherapy and psychotherapy. It is the purpose of this presentation to acquaint the reader with the techniques of fluid balance associated with burns used at the Hospital of the University of Pennsylvania. Obviously, this represents only a single facet of a huge problem. In the actual care of patients many problems require simultaneous consideration, and this fact should never be lost sight of in the following discussion. Better application of the knowledge gained of fluid and electrolyte balance should permit the greatest number of seriously burned children not only to survive, but also to present in optimal condition for early skin grafting.

First Aid

The initial step in the care of a burned patient is to cover the burn wound in order to prevent contamination and to alleviate pain by preventing air from coming in contact with the injured surface. The patient should then be transported to a physician's office or hospital, using a clean sheet or cloth as an emergency dressing. Stimulants should not be used. Oral intake is to be avoided. In the case of chemical burns, all corrosive material should be washed immediately with copious quantities of water in order to get rid of the injurious agent. All clothing should be removed.

Evaluation of the Seriousness of a Burn Injury

The severity of the burn injury can be assessed satisfactorily, since it depends on only two principal factors: percentage of body surface burned and depth of burn. Additional factors determining the seriousness of a burn include its location, the age and physical condition of the patient, and the presence of concomitant injury. A severe burn is one which is sufficient to produce shock and may later require grafting. A child under the age of 6 years with as little as 8 per cent partial thickness burn may require parenteral therapy. More than 15 per cent involvement may be equally serious in a child 6 to 12 years. These are in contrast to greater than a 20 per cent area of equal seriousness in the adult. The depth of involvement is important in that a considerably smaller area of full thickness (third-degree) burn may be equally serious. Flame burns are more apt to produce deep involvement than hot liquid scalds. More anemia, both early and late, seems to follow third-degree burns of any extent.

In an attempt to estimate the extent of total body surface injured,

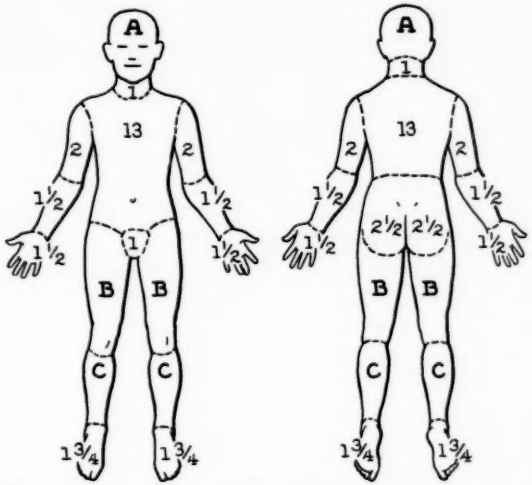

Fig. 29. Relative percentage of areas affected by growth. (After Lund and Browder.[8])

Age in years:	0	1	5	10	15	Adult
A = ½ of head	9½	8½	6½	5½	4½	3½
B = ½ of thigh	2¾	3¼	4	4¼	4½	4¾
C = ½ of 1 leg	2½	2½	2¾	3	3¼	3½

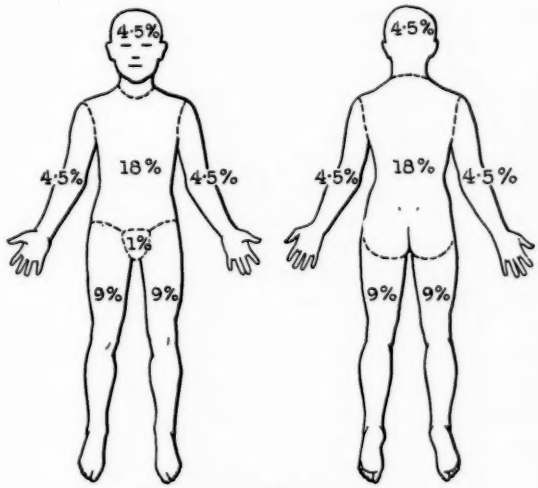

Fig. 30. The rule of nines.

Berkow[2] in 1924 presented data on percentage of surface areas of various parts of the body. Lund and Browder[8] found that the Berkow tables were not applicable to all ages. They determined the changes in percentage of body surface of various parts that occur during different stages of development from infancy through childhood (Fig. 29). The area of the head makes up a relatively large proportion of the total skin area of infants as compared with the findings in adults. This disproportion is counterbalanced in infants by the smaller proportionate area of the thighs and legs. The proportion of skin of all other parts is essentially the same at all ages.

Correct estimation of the extent and depth of injury is difficult when a patient is first seen. Usually the area is exaggerated and the depth underestimated. The extent of the burn, so far as this affects therapy, might be calculated satisfactorily from a modification of the rule of nine (see Fig. 30) if one allows relatively more for the head (almost two times) and less for the legs (about half) in children under five years.

Initial Procedures

The initial steps in care of the burned patient must be planned carefully. If two or more physicians can attend the patient, the procedures may be carried out with greater dispatch. The patient's clothing should be removed as soon as possible after admission to the hospital. A brief history should be obtained from the patient or family of how the burn was incurred and of the possibility of other types of injury, plus a review of the general medical status of the patient before the accident. It is advantageous to weigh the patient as soon as his clothes are removed and before putting him to bed. If this is not possible, the parents' estimation of the child's weight plus an opinion based on general size and age should be used as a base line for fluid therapy. It is extremely important from the beginning to reassure the patient. An immediate assessment of the patient should then be made to determine whether a tracheostomy is required. This is particularly applicable in burns about the head and neck region and those of the respiratory tree itself.

Even though pain is not a prominent feature of extensive deep burns, a small dose of a narcotic agent is beneficial when given intravenously. *Narcotics should never be given subcutaneously,* since absorption is poor, owing to circulatory deficiencies, and as a result a depot of narcotic will be built up in the subcutaneous tissue only to overwhelm the patient when circulation is restored to normal. A good rule of thumb for dosage of morphine in children is 1 mg. for each 10 pounds of body weight. The morphine should be diluted in 3 to 5 cc. of saline solution

and injected intravenously over a period of 1 to 2 minutes. If it is felt that the burn is severe, an intravenous lifeline should be established immediately and the morphine given through this indwelling polyethylene catheter. The usual site for placement of the catheter is in the saphenous system at the ankle, or the femoral system at the groin.

At the time the cut-down is established blood should be drawn for laboratory determinations, cross matching, and so on. Fluids may be started immediately, giving saline until an adequate program can be calculated. In addition, antibiotics in the form of penicillin and streptomycin should be administered promptly and continuously, as well as a dose of tetanus antitoxin or toxoid. After these initial procedures have been carried out a complete chart should be prepared to serve as a work sheet for the first 48 hours of therapy.

Rationale for Fluid Replacement

Edema is an inevitable sequel of burning. Two fundamental factors involved in its production are vasodilatation and increased capillary permeability to proteins. In a first-degree burn vasodilatation is the only change that occurs. Protein losses are insignificant, and edema is barely perceptible. A second-degree burn is characterized not only by more severe capillary damage, but also by damage involving a larger mass of tissue than a first-degree burn of the same extent. A large amount of fluid can accumulate beneath the surface of the wound before any visible swelling occurs. Leakage of proteins is observed in areas that receive the most heat, while only hyperemia occurs in areas subjected to less heat. In third-degree burns the entire thickness of the skin is destroyed, and capillaries are thrombosed close to the surface of the wound. This has a twofold effect: erythrocytes are removed from the circulation, producing anemia, and fluid exchange ceases. As to the rate of fluid loss, Cope's[5] investigations have revealed that losses are incurred most rapidly early after burning. The rate of edema formation then declines, and fluid losses finally cease about 48 hours after burning, at which time edema is maximal.

Resorption of edema fluid occurs chiefly by way of lymphatic drainage. In more extensive burns the wound edema may persist for two or three weeks. This delay in excretion of the fluid occurs characteristically in deep, extensive burns and especially those complicated by invasive infection. Fluid redistribution is a complex and unpredictable event.

By measuring the composition of blister fluid and lymph drainage from burned areas Cope and Moore concluded that the protein lost is always of a lower concentration than that of the plasma, with slightly more albumin exuded than globulin, owing essentially to the relative size of the molecules. The increased protein content of lymph is a

result of capillary damage and not merely a reflection of tissue lysis with the release of plasma proteins. There is evidence to indicate that one of the early changes after thermal injury is an increase in the protein concentration in the plasma. Although proteins are lost from the plasma into the burn wound, water and electrolytes are lost more rapidly, increasing the plasma protein concentration.

Water and electrolytes freely permeate the normal capillary. Burning affects water and electrolyte shifts by increasing capillary hydrostatic pressure and protein shifts. Injury to tissue cells may be another important factor in the movement of water and electrolytes.

Using mice, Fox[7] noted loss of potassium from burned tissues and its apparent uptake in unburned tissues. This loss of potassium was accounted for quantitatively by an increase in sodium in the burned tissues over and above that expected on the basis of interstitial edema. These data suggest that sodium is lost into burned tissue by the entrance of sodium into injured cells as well as by body accumulation of interstitial edema. Hypo-osmolarity of the extracellular fluid could be a consequence of the sodium shift into injured cells, and water would, therefore, shift into unburned tissues. Thus a twofold fluid loss may occur: at the site of injury and in unburned tissue cells.

Regardless of the exact mechanisms involved, the need for sodium therapy in burns is indisputable. Experimental deep burns are characterized by a transient hyperkalemia which appears to result both from the release of potassium by burned tissue and from hemolysis of erythrocytes. Potassium changes, however, during the first 24 hours after burning are of little practical clinical significance, and solutions containing potassium in more than minute quantities should certainly not be given during this interval.

In general, red blood cell destruction is a significant problem only in connection with deep burns. Red cells are trapped in the burned area at the time of injury and are hemolyzed there. In addition, thrombosis of blood occurs in the capillaries of burned tissue and contributes to the decrease in red blood cell mass. The clinical importance of red blood cell destruction was emphasized by Abbott[1] and Evans,[6] who found that seriously burned patients frequently had severe anemia after the period of fluid redistribution. They pointed out also that once anemia is established, it is difficult to correct by blood transfusions and that replacement should therefore be carried out during the early days of treatment. From a clinical standpoint it is wise to assume that in a severe burn the red blood cell destruction is approximately 10 to 15 per cent of the red blood cell mass in the first 48 hours. The best guide to therapy at present is that the deeper and more extensive the burn, the greater the amount of transfusion required.

Renal function may be altered as a result of several factors. With delayed or inadequate replacement therapy effective renal plasma flow may decrease to one tenth or less of normal within minutes to a few hours after a burn. The usual response to severe stress results in sodium

and water retention and failure to conserve potassium. Finally, morphine or barbiturate therapy may lead to an increase in antidiuretic hormones, and inability to excrete excess water with signs and symptoms of water intoxication.

Program of Fluid Therapy

In 1952 Evans[6] introduced his formula, which has served as an invaluable and practical guide to the fluid therapy of burned patients. We have adopted this regimen, recognizing its deficiency in not making allowance for the depth of burn.

As a basic allotment, the patient is given 1 ml. of colloid (blood, plasma, dextran, and the like) per kilogram of body weight for each per cent of body surface burn, 1 ml. of electrolyte solution (physiologic saline solution, Hartman's solution, and so forth) per kilogram of body weight for each per cent of body surface burned, and approximately 200 cc. of 5 per cent glucose in water per kilogram of body weight up to 2000 cc. in order to cover the normal daily requirements for insensible loss and urine volume. This program should cover the first 24 hours following burning, modified, of course, by the patient's general condition, the hematocrit, and the urine output and specific gravity. About half of this should be given within the first 8 hours and the remainder over the next 16 hours as a continuous infusion. One of the most important factors in successful fluid replacement in children is a careful and frequent check of the amount infused. Since it is impossible to do with the usual 500-cc. or 1-liter flasks commonly used, we have used a small buret containing at a maximum 200 to 250 cc. graduated in 10-cc. increments so that the child may not receive too rapid an infusion even if it "runs away." The volume of infusion should be checked at 30-minute intervals by a member of the nursing staff or by an attending physician so that any readjustment in the rate of fluid absorption can be made.

One should endeavor to keep the urine output above the minimum hourly output for a child of corresponding age (Table 22). One can readily see that above the age of one year a good rule of thumb is 20

TABLE 22. *Fluid Intake and Normal Daily and Hourly Urine Excretion*

AGE	FLUID INTAKE, 24 HOURS	URINARY EXCRETION PER HOUR
0–12 months	200– 500 ml.	8–20 ml.
1–4 years	500– 575 ml.	20–24 ml.
4–7 years	575– 650 ml.	24–28 ml.
7–10 years	650– 725 ml.	28–30 ml.
10–12 years	725– 800 ml.	30–33 ml.
Adult	1500–2000 ml.	50 ml.

to 25 cc. per hour. An indwelling catheter will greatly aid in the process of urine collection and estimation.

Some precautions are pertinent. In burns over 50 per cent of the body surface one calculates as if only 50 per cent of body area were burned. Secondly, during the second 24-hour period one should administer approximately half of the volume of colloid and electrolyte given during the first 24 hours while infusing the same amount of non-electrolyte solution in order to maintain insensible loss and urine volume.

Choice of Electrolyte Solution. One is tempted to give sodium chloride in 0.9 per cent solution (physiologic or normal saline) as the colloid of choice, since it is inexpensive and available at most institutions. However, this is far from an ideal replacement solution, since it contains an excessively high concentration of chloride and, when administered to children in large doses, is associated with a hyperchloremia, an undesirable and unnecessary complication (hyperchloremic acidosis). A more acceptable balance solution can be obtained by mixing 2 volumes of 0.9 per cent saline solution and 1 volume of sixth-molar lactate solution. In addition, there are many prepared solutions on the market of a balanced nature, e.g., Hartmann's solution.

In the choice of colloids there is much debate among the authorities in burn treatment as to the exact proportion of blood and plasma which should be administered a burned patient. Moyer believes that no colloid solution other than blood is ever required. Quinby and Cope,[11] on the other hand, believe that the present tendency may be to give too much blood. The authors have demonstrated a close relationship between hematocrit and blood viscosity and point out that the high viscosity increases the work load of the heart. According to their observations, periodic hematocrit determinations should be obtained, and, if the hematocrit level is 60 or above, vigorous therapy with fluids other than blood should be instituted. Clinical appraisal of the patient and periodic hematocrit determinations will suggest an adequate ratio of blood to plasma or blood to dextran in the particular patient. Dextran in saline, a plasma volume expander, has been of definite clinical value, particularly for burns that are predominantly second degree, in which most of the colloid requirements can be met by dextran or dextran and plasma.

Generally it is preferable not to give anything by mouth for the first 48 hours in extensively burned patients. If thirst is overwhelming, small amounts of water may be administered, but the amount of water which the patient drinks must be measured and recorded. Frequent examination of the abdomen is desirable, since acute gastric dilatation is a common complication of burns and may prove fatal unless it is promptly recognized and treated.

Fever (101 to 103° F.) is not uncommon. The temperature response is a nonspecific effect of injury, but may represent a sign of early infection. Accordingly, it is important to check the patient's temperature frequently and observe him carefully for early signs of infection.

After the initial 48 hours of fluid therapy there may develop a more pronounced picture of toxicity which is poorly understood. Although adrenal cortical exhaustion has been posed as an explanation for this period of toxicity, replacement therapy has not satisfactorily combated it. Hyponatremia may be noted, and water intoxication may be suggested by salivation, vomiting, twitching and convulsions. Another danger of this period of burn therapy is that of pulmonary edema arising when fluid at the wound site begins to be reabsorbed. For this reason stringent fluid restrictions have been advocated. In recent years, however, it has become evident that although restrictions of electrolytes are essential, large quantities of water may be required.

TRAUMA AND SHOCK

Trauma to any person, especially a child, evokes a systemic response. Moore[10] and others have defined the sequence of events following trauma, stressing the role of the pituitary-adrenal axis. The consequence of bodily trauma may often be a shocklike state characterized by persisting deficiency in blood flow to tissues throughout the body. Unless this syndrome of shock is treated intensively, it progresses by various mechanisms to a fatal outcome. Whether it is due to blood volume deficiency or severe infection in the absence of blood volume deficit, our primary mode of treatment is that of blood volume replacement plus drug therapy to stabilize the peripheral vascular tree. The vital organs concerned in trauma and shock, including the central nervous system, heart, liver, kidney and the adrenal cortex, must all be considered in planning a program to help the patient. In the brief discourse which follows only the highlights of trauma and shock therapy can be reviewed.

Fluid Therapy in Trauma and Shock

When examining the severely injured child, it is necessary to work rapidly with a preconceived plan of action.

Initially it should be ascertained whether the airway is adequate. If there is any question of patency, a tracheostomy should be done. Sucking wounds of the chest should be closed, and then active bleeding should be stopped. In any seriously injured patient a venous cut-down should be performed and a suitably sized polyethylene catheter inserted. At this time hemoglobin, hematocrit, cross matching and any other necessary chemical determinations can be obtained. In smaller children

it is of value to have the usual 500-cc. bottles of blood divided into smaller containers, usually 50- or 100-cc. bottles. In this way small but necessary transfusions can be performed without undue waste of blood or overtransfusion.

Careful examination of the patient should be performed rapidly, noting especially pupillary reflexes, state of consciousness, fractures, evidence of soft tissue trauma, chest and abdominal examination with all the findings recorded along with the time of examination. If the patient is in shock, it is important to determine the causative agent when possible, considering factors such as excessive blood loss either from external or internal bleeding due to a ruptured viscus, peritonitis, pneumothorax, fractures, and so on. An emergency cross match can be requested if blood loss has been severe, but colloid replacement should be started before blood becomes available. Plasma, preferably of the individual donor type prepared by allowing it to stand at room temperature for six months, is useful. Plasma volume expanders (dextran) are valuable, especially when plasma is unavailable. Repeated small transfusions are of more value than a single large one and permit careful follow-up of the patient.

The patient should give a specimen of urine as soon as practicable, and this should be examined for evidence of bleeding, which often gives a clue to trauma to the kidneys or bladder. If a specimen cannot be voided, catheterization should be carried out, especially when injury to the bladder or kidneys is suspected. In shock it is useful to have the bladder catheterized to help in deciding whether fluid replacement is adequate.

Open fractures should be dressed and immobilized to prevent further damage; other fractures can be immobilized after definitive initial treatment has been started. Careful repeated examinations should be made to detect intracranial injury and intraperitoneal bleeding. *Necessary* x-rays can be taken when the patient is being transferred to bed, but these must be kept to a minimum.

One cannot follow any set formula in determining the fluid requirements of a traumatized child. Obviously this will depend on the type and severity of injury, the age of the patient, the presence of vascular injury, whether or not a burn is also present, and the general state of health. Several general precepts may be of value in dealing with this problem.

1. Avoid excessive use of saline.
2. Avoid use of potassium until the urinary function is adequate.
3. Avoid overtransfusion.
4. Avoid subcutaneous infusions.
5. Avoid excessive alkalis which may lower the ionized calcium and produce tetany.

6. Use frequent small transfusions.

7. Do not hesitate to give more blood or fluids than had been calculated initially if the urinary output falls to a low level.

SUMMARY

In children, burns and other trauma may produce a shocklike state in situations which might appear trivial in an adult. In view of the rapidity of the development of shock, intensive therapy should be started early after traumatic episodes. A plan of therapy for the burned child as well as the child involved in other types of trauma is presented. The use of whole blood and other colloid substances and electrolyte solutions is emphasized. The importance of understanding the pathophysiology of traumatic situations is stressed so that a definite step-by-step plan of therapy can be formulated and carried to a successful conclusion.

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3400 Spruce Street
Philadelphia 4, Pennsylvania

FLUID THERAPY IN NEWBORN INFANTS

HELEN SEIBERT REARDON, M.D.

The bases for the planning of fluid therapy are the same for infants and children of any age. Initially the need for fluid therapy is established by clinical evaluation and by laboratory studies. The quantities of fluids and electrolytes are calculated on the basis of daily obligatory expenditures and of any deficits which have accrued from unusual losses and/or from inadequate intake. During the first three to four days of life the calculations for obligatory expenditure must be modified in relation to the limited needs at this age.

ESTIMATION OF FLUID AND ELECTROLYTE NEEDS

The estimation of fluid and electrolyte needs of an infant depends upon clinical appraisal and laboratory studies at frequent intervals. Clinical evaluation is the more important, both for diagnosis and for treatment.

Clinical Appraisal

It is difficult to evaluate clinical changes in newborn infants because of their tremendous variability. It is questionable whether newborn infants become critically ill as fast as is generally believed or whether our inability to evaluate early clinical changes is at fault. The early signs of pneumonia such as increase in rate, diminished breath sounds and the like may be overlooked or absent in some infants. Usually attention is directed by the fact that the infant is not doing well, has fever or a subnormal temperature (more common than fever) or is not feeding well. The differentiation between dyspnea or hyperpnea, thirst and

From the Department of Pediatrics, Temple University School of Medicine, and St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.

hunger, and true vomiting and "spitting" may be most difficult to ascertain.

History is usually obtained from the nurses, who must have excellent training, because their astute observations are often the guide to both the early diagnosis of difficulties and the subsequent response to therapy. The type, duration and systemic effects of the illness—such as anorexia, vomiting, change in crying or sucking reflexes, activity and muscle tone, increased or decreased urination, fever or subnormal temperature, changes in respiration, color, weight and character of stools—may be important clues in evaluation of the onset of an illness. The usual signs of severe dehydration (extreme weight loss, sunken fontanel, poor tissue turgor) are late manifestations of illness. Shock may occur before all the severe signs are apparent.

Thus early and frequent clinical re-evaluation may not only prevent the occurrence of severe losses by prompt recognition of the cause and institution of appropriate therapy, but is also important in assessing the results of therapy.

Laboratory Data

If the variations and limitations of laboratory studies are appreciated and correctly interpreted, blood chemical studies can be of inestimable

TABLE 23. *Plasma Chemical Studies of Full Term and Premature Infants*

	AGE IN HOURS	pH	CO_2 mEq./L.	$BHCO_3$ mEq./L.	pCO_2 Mm. Hg (Calculated)
Full term	1	7.30	20.0	18.8	39.1
	24	7.38	20.5	19.5	33.4
	96	7.39	22.5	21.4	36.4
Premature	48–72	7.31	20.3	19.4	38.9

aid in evaluation of the diagnosis, clinical course and subsequent requirements for fluid therapy.

VARIATIONS OF BLOOD CHEMICAL PATTERNS. The averages and ranges of values for plasma chemical studies in well full term infants are recorded in Table 23. It is apparent from these data that full term infants exist in a state of compensated metabolic acidosis through the fourth day of life as manifested by their decreased carbon dioxide content. Premature infants may remain in a state of relative acidosis for several weeks, with decreased values for both plasma pH (average 7.30) and carbon dioxide content (20.0 mEq. per liter). Only 10 per cent of well premature infants have an adult type of blood chemical pattern, though they grow and behave in a perfectly normal fashion.[14] The values for plasma potassium in well full term and premature infants through the first 4

days of life may vary from 5.0 to 7.0 mEq. per liter;[10, 11, 13] for chloride, from 104 to 112 mEq.[8, 11, 13, 14] Determinations of plasma sodium in full term infants are variously reported as elevated with an average value of 152 mEq. per liter in the first 2 days of life;[2] or within the normal range of 135 to 140 mEq.[11] Premature infants may have somewhat lower values for sodium of 134 to 135 mEq. per liter on the first day of life[13] and a range from 137 to 145 mEq. throughout the first 3 days.[11] Thus the variation of certain chemical studies in well infants must be appreciated before any attempt is made to correct fluid and electrolyte deficits in sick infants. For example, it is not practical to attempt a correction of carbon dioxide content to the normal adult level by fluid therapy.

TABLE 24. *Laboratory Data*

Blood	Hemogram
	Chemical:
	Plasma pH, CO_2 content and Cl
	Plasma or serum K and/or EKG
	Osmolarity—Na or osmotic pressure
	BUN, hematocrit and protein
Urine	Analysis
	Output (volume)
	Electrolytes
Cultures	As indicated

It is also possible that one of the reasons why sick premature or full term infants may become severely dehydrated and acidotic is that they are in a state of mild acidosis at the onset of an illness. Another probable contributory factor is inability to concentrate urine as well as adults can during severe degrees of water deprivation.[16]

LIMITATIONS OF BLOOD CHEMICAL DETERMINATIONS. Blood chemical determinations reflect direct changes in the vascular compartment (5 to 10 per cent of the body fluid), but not of the intracellular space. Changes in the intracellular compartment can be estimated by clinical evaluation of the patient and a knowledge of changes usually produced by the specific disease entities. For example, it is possible to have normal values for sodium and potassium in plasma, when there is an actual decrease of intracellular electrolytes. In addition, blood chemical analyses measure the chemical changes only at the moment the blood was obtained and do not reflect sequential changes.

The type of laboratory data which may be indicated is shown in Table 24. The hemogram is most helpful in the diagnosis of anemia, thrombocytopenia or erythroblastosis. A significant leukocytosis after the first week of life may indicate infection.

Plasma pH and carbon dioxide aid in evaluation of the type and extent of acid-base deviations. By clinical evaluation alone it is im-

possible to anticipate the extent or type of these deviations in newborn infants. Although newborn infants may have the clinical manifestations of hyperpnea which would indicate either metabolic acidosis or respiratory alkalosis, dyspnea is a more frequent finding. Change in the value of plasma sodium, the most stable blood electrolyte, is a good indication of excessive plasma water, sodium depletion or sodium excess. Low plasma sodium is usually due to water excess, true salt depletion or underlying renal disease. Determinations of plasma sodium correlated with determinations of osmotic pressures by serum freezing point depression will aid in the differentiation. Since the technique for determination of osmotic pressure is usually not available, careful weighing of the patient correlated with the clinical history and examination and laboratory findings will usually lead to the correct interpretation of changes of sodium values. Shifts of plasma chloride are more difficult to interpret. Plasma chloride may represent absolute deficits or increases in chloride, or only reflect changes in value for other anions. Values for plasma chloride must be correlated with carbon dioxide content and sodium, for better interpretation of specific variations.

Deviations of hematocrit values may indicate variations in the volume of vascular fluid or anemia. The hematocrit is usually more helpful in estimation of the degree of dehydration than are determinations of blood urea nitrogen in the first few days of life.

It is difficult to collect urine from newborn infants, but the newer type of collectors[9] have lessened the problem. Urinalyses serve as an important guide in the diagnosis and treatment of many metabolic problems such as the adrenogenital syndrome, diabetes mellitus and galactosemia.

Finally, cultures of stool, urine, blood and nasopharyngeal or cerebrospinal fluid may be indicated if signs of infection are present.

INDICATIONS FOR FLUID THERAPY

Fluid therapy may provide fluid, electrolytes and calories for (1) the daily obligatory expenditure or maintenance requirements; (2) the replacement of deficits which have been incurred as the result of lack of intake, abnormal losses or both; (3) the replacement of continual unusual losses; (4) supplemental therapy in which a specific physiologic function is involved, i.e., induction of diuresis; or as a vehicle for specific therapy, e.g., for intravenously administered "sulfa" drugs.

Obligatory Expenditure

The fluid, electrolyte and caloric requirements for daily maintenance of full term infants before the third day of age are practically negligible

unless undue losses occur as the result of disease. This assumption is based on the premise that breast-fed, well, full term infants have a low intake (about 4 to 10 cc. per pound) of colostrum before the third day of life. The average values for the sodium and potassium content of colostrum[1] are about 20 mEq. per liter. On the third and fourth days of life the intake increases sharply to an average of 20 cc. and 40 cc. per pound respectively.[18] The fact that well infants can take more fluid has been demonstrated by the common practice of starting infants on a diluted milk formula at 24 hours of age.

The maintenance requirements for well premature infants during the first few days of life are less well defined than are the requirements of full term infants. There is lack of agreement about the needs of well

TABLE 25. *Daily Caloric Requirements*

	BASAL CALORIC REQUIREMENTS	USUAL CALORIC REQUIREMENTS
	Calories per kilogram	
Full term infants (1–7 days)	49*	
Premature infants (1–7 days)	53*	
Young infants to 1 year	60–55	120–100
Older infants (2–3 years)	55	100–90
Children to 12 years	55–40	90–70
Adolescents and adults	30–25	70–45

* Data of H. H. Gordon and S. Z. Levine.[6]

Adjustments:

1. Decrease or increase in temperature leads to decrease or increase in caloric expenditure of 12% per degree C. (8% per degree F.)
2. Usual bed activity causes an increase of 20–30%.
3. Growth and S.D.A. may be ignored for practical purposes while on short-term parenteral fluid therapy.

premature infants for fluids, electrolytes and calories after 24 hours of age. We have interpreted the limited available data[15] to indicate that sufficient fluid, electrolytes and calories are required after 24 hours of life by premature infants to provide for basal needs in contrast to the almost negligible requirements of full term infants. These requirements are calculated in the same manner as for full term infants after the first four days of life.

After the first three to four days of life the daily obligatory expenditure for full term infants and probably for premature infants of any age may be established by the method of Darrow and Pratt.[4] This method is based upon the principle that fluid and electrolyte requirements are proportional to the caloric expenditure of the patients.

The caloric expenditure may be derived from Table 25, which relates weight to the basal metabolic rate, plus increments for fever, activity, specific dynamic action, and growth. The figures which refer to the

caloric expenditure of full term and premature infants are not true basal values, but are values for sleeping infants after a feeding. However, they are practical measurements for use in computing the minimum fluid requirements for infants on a low caloric intake who receive parenteral fluid therapy. For example, a sick newborn infant weighing 3 kg. who requires parenteral fluids may be considered at or slightly above a basal caloric expenditure of 180 calories per 24 hours, whereas the same infant on a full diet even with some restriction of activity may be considered to be at "usual" requirements of about 360 calories per 24 hours.

The daily obligatory expenditure of water which is equivalent to the insensible water loss, urine and stool losses in cubic centimeters may be

TABLE 26. *Daily Water and Electrolyte Requirements per 100 Calories Metabolized*

OBLIGATORY WATER EXPENDITURE	CC.	SODIUM mEq.	CHLORIDE mEq.	POTASSIUM mEq.
Insensible water loss	42			
Sweat (without fever and low environmental temperature)	15–20	0.5	0.5	0.2
Sweat (with fever or environmental temperature over 90° F.)	50–70			
Stool (normal)	4	0.1	0.1	0.4
Urine (fasting with low CHO intake, Sp. Gr. 1.012)	60	0.2–3.0	0.2–3.0	0.4–2.0
Urine (breast milk feedings, Sp. Gr. 1.012)	60–65			
Urine (formula feedings 20 cal./oz., Sp. Gr. 1.012)	75–80			
Water of metabolism	12			

Reconstructed from the data of D. C. Darrow and E. L. Pratt.[4]

calculated from Table 26, which relates the water expenditure in cubic centimeters to 100 calories metabolized per 24 hours. Water available for expenditure is equal to the intake plus the water of oxidation. The latter is relatively low in parenterally fed infants and may be disregarded. Thus the infant mentioned above who needs parenteral fluids and has no abnormal losses requires about 120 cc. per 100 calories metabolized or about 215 cc. of fluid in 24 hours. This is derived by the summation of 60 cc. per 100 calories metabolized for insensible loss, stool and mild sweating plus 60 cc. per 100 calories metabolized for urinary losses (assuming a urine concentration of 1.010 to 1.015). Formula-fed infants receiving a full diet require an extra 20 to 25 cc. per 100 calories metabolized, or a total of 140 cc. per 100 calories metabolized per day for increased excretion of end products of protein metabolism and electrolytes. In other words, infants with a low metabolic turnover, existing at or below basal caloric requirements, and without excessive losses, require

less water (about 30 cc. per pound per 24 hours or 60 cc. per kilogram per day) than do infants who are well, active and receiving an isocaloric formula and need 75 to 90 cc. per pound per 24 hours (200 cc. per kilogram).

The obligatory loss of electrolytes is not clearly defined in newborn infants. Present information indicates that premature infants have no difficulty in excreting sodium and chloride,[7] potassium and bicarbonate[18] in the urine. It does not follow that infants can excrete an excess of these electrolytes as well as do adults. However, the figures given in Table 26 for excretion of milliequivalents of electrolytes per 100 calories metabolized probably can be used for the calculation of obligatory expenditures of electrolyte in the same manner as that used for expenditures of fluids. The obligatory expenditure of electrolytes is usually met by a fluid containing 30 mEq. of sodium chloride and 15 mEq. of potassium chloride per liter of solution when the amount required for size or caloric expenditure is administered.

Increase or Decrease in Daily Expenditure

Adjustments for increases or decreases in daily fluid or electrolyte expenditure must be made for any infant regardless of age.

An increase in expenditure of fluid may occur as the result of persistent hyperpyrexia, hyperventilation or polyuria. Although severe hyperventilation is unusual in the first few days of life, the losses by this route may be increased fourfold to fivefold and may require an additional 50 to 75 cc. per 100 calories metabolized per 24 hours. Losses from sweat induced by changing environmental temperature from 80 to 90° F. or from fever may double or triple the water losses from the skin. The need is determined by repeated clinical appraisals and frequent determination of weight changes. When possible, measurements of the volume of urinary losses with determination of specific gravity also will aid in evaluation of the fluid requirement.

The concentration of electrolytes in the sweat usually depends upon the activity of the adrenocortical hormones, except possibly in fibrocystic disease of the pancreas. The quantities of electrolytes lost in urine or sweat may be determined by direct collection and analysis of the electrolyte content of the fluid. For example, levels of sodium above 90 mEq. per liter and chloride above 60 mEq. in sweat are abnormal.[5]

The electrolyte content of "Wangensteen drainage fluid" may be determined or an estimation of the content can be made from Table 27. Losses may be corrected by the intravenous administration of an equal volume of fluid for that which was lost. The fluid should be composed of 3 parts of isotonic saline solution and 1 part of water to which potassium chloride, 0.15 to 0.2 gm. per cent, may be added.

TABLE 27. *Electrolyte Content of Gastrointestinal Fluids*

	H	Na	K	HCO_3	Cl
		Milliequivalents per Liter			
Gastric	40–60	20– 80	5–20		100–150
Biliary		120–140	5–15	30– 50	80–120
Pancreatic		120–140	5–15	70–110	40– 80
Small bowel		100–140	5–15	20– 40	90–130

Reconstructed from the data of R. E. Cooke and L. G. Crowley.[3]

Ileostomy and colostomy dressings may be weighed to approximate loss of fluid, but the electrolyte content is either replaced on the basis of the known values (Table 27) of the intestinal contents or in a manner similar to that used for "Wangensteen drainage" and correlated with frequent checks of the clinical status and of the blood chemical pattern.

Internal hemorrhage or other loss of blood may be estimated by hemoglobin and hematocrit determinations at frequent intervals.

Fecal losses of water and electrolytes due to diarrhea are the most difficult to estimate. Weights obtained before and after a bowel movement or weighing of stools are not easily accomplished, but are necessary in chronic diarrhea. Darrow and Pratt[4] have noted that the electrolyte concentration per kilogram of stool may vary from 12 to 90 mEq. of sodium, 10 to 110 mEq. of chloride and 10 to 80 mEq. of potassium. In the usual type of infantile diarrhea the sodium and potassium losses always exceed the chloride loss. Fortunately, the substitution of parenteral fluid therapy for oral feedings usually reduces the stool loss in acute diarrhea to negligible quantities.

A decrease of expenditure of fluids is usually associated with changes in the external environment or with diminished renal output. The use of high humidity in an incubator may reduce loss of water by 20 to 50 per cent. Decreased renal output may be due to renal disease, central nervous system disease or excessive extrarenal water loss which reduces the amount of water available to the kidneys. About half of the total fluid necessary to satisfy the obligatory expenditure of water will be excreted by the kidneys. Therefore proportionate adjustments in fluid intake must be made when there is a reduced output of urine associated with renal disease or with central nervous system disease such as meningitis. Meningitis may be associated with oliguria for reasons not yet known.[12] Regardless of the cause of oliguria or anuria, potassium should not be given if there is any doubt about the adequacy of the renal output. If oliguria is due to an extrarenal cause such as diarrhea, the calculated deficit requirements for replacement of sodium chloride and water are administered, and, when the oliguria is corrected, potassium may be given. If the oliguria or anuria is due to renal disease,

sodium, potassium and chloride are not administered, and the total fluid intake must be reduced. If sodium must be used for correction of severe acidosis, it is administered in the form of sodium bicarbonate.

In summary, undue change in weight correlated with clinical examination and laboratory studies is the best guide for the estimation of abnormal loss of fluid and for the evaluation of therapy.

Therapy for Previously Incurred Deficits

Prompt recognition and treatment of a specific disease will prevent the accumulation of deficits. For example, if intestinal obstruction is recognized within 24 hours of birth, losses will be minimized, and fluids will not be needed for replacement of deficits before operation. However, if the same disease is unrecognized for several days, rather severe deficits of both fluid and electrolytes will ensue, which will require immediate replacement.

The replacement of fluid and electrolyte deficits is calculated on the basis of body weight. A loss of weight in excess of 1 per cent is usually considered to be abnormal except in the first 4 days of life. In acute dehydration a loss of weight greater than 1 per cent may be assumed to be due to fluid loss. In any chronic entity such as pyloric stenosis, in which symptoms have been present for one or two weeks, weight loss is also due to starvation. The average newborn infant usually regains his birth weight by 7 to 10 days of life. The lowest part of the weight curve is usually on the third or fourth day of life. Therefore, if the weight of an infant continues to decrease with or without adequate intake of fluids, it may be assumed that there are cumulative losses. Thus change in weight is the best guide for estimation of rapidly acquired deficits. If this information is not available, 5 to 10 per cent of the present weight may be used as a rough guide for the calculation of losses associated with clinical evidence of moderate or severe dehydration.

The majority of diseases which cause acute dehydration in the newborn period are associated with isotonic or hypotonic dehydration. Infants with diarrhea are an exception to this generalization; they may have hypertonic dehydration. It may be assumed that at least 50 per cent and possibly more of any rapidly occurring weight loss represents fluid loss from the extracellular compartment. Therefore an amount of fluid equal to the extracellular loss must be added to the 24-hour requirements for obligatory expenditures. Thus if the infant with a known weight of 3 kg. loses 300 gm., at least half of this amount (150 cc. of fluid) should be added to the initially estimated 215 cc. requirement for maintenance. A total of 365 cc. would then be the minimum fluid requirement for 24 hours (55 to 60 cc. per pound or 130 cc. per kilogram). Adjustments for daily losses may require an increase in this

amount by 30 cc. per pound (60 cc. per kilogram). However, it is seldom necessary to exceed a total of 80 to 90 cc. per pound (180 to 200 cc. per kilogram) of fluid per 24 hours for both obligatory expenditures and replacement of all deficits. Moderate to severe hypotonic dehydration ordinarily requires 5 to 10 mEq. of sodium per kilogram per 24 hours for replacement; isotonic dehydration, 5 mEq. per kilogram; and 3 mEq. of sodium per kilogram per 24 hours is usually adequate for hypertonic dehydration. Thus the infant weighing 3 kg. with severe hypotonic dehydration may require 20 to 30 mEq. of sodium per 24 hours for correction of previous deficits plus 2 to 3 mEq. for basal needs.

Initial therapy is usually directed toward expansion of the extracellular space with an isotonic solution such as 20 cc. per kilogram of Ringer's lactate solution, or 5 per cent glucose in isotonic saline solution. If the infant is in a state of shock, this fluid may be administered rapidly and should be followed by a blood transfusion of 10 to 20 cc. per kilogram.

Subsequent hydration of the extracellular and intracellular compartments is accomplished by slower correction with an appropriate solution which should contain the remainder of the estimated electrolyte and fluid requirements for a 24-hour period. Most often such fluids should be hypotonic in respect to their electrolyte equivalency, in order to provide for continuous replacement of electrolyte requirements over the total 24 hours. If severe acidosis is present, plasma pH less than 7.10 or carbon dioxide content less than 10 mEq. per liter, part of the 24-hour requirement for sodium may be given as an intravenous solution of 3.75 per cent sodium bicarbonate (0.5 gm. per kilogram), or as sixth-molar sodium lactate, 30 cc. per kilogram. (There is some doubt as to the efficacy of lactate solutions for the treatment of acidosis in premature infants.)

The addition of potassium to parenteral fluids is seldom necessary when such therapy is needed only for a short time, and potassium should not be added under any circumstances until renal output is adequate. Potassium is indicated when there is metabolic alkalosis and in other situations in which there is a deficit of this electrolyte. The concentration of potassium should ordinarily not exceed 20 mEq. per liter, with a total amount of 3 mEq. per kilogram per 24 hours. Potassium should not be used in the fluid therapy of premature infants during the first few days of life unless there is positive laboratory evidence of deficiency, since these infants usually have high plasma levels during this period.

With the initial replacement of extracellular fluid and electrolyte losses in the first 24 hours, subsequent requirements are sharply reduced to that necessary for obligatory expenditures and replacement of abnormal daily losses.

CONCLUSIONS

The prevention of severe deficits of body water and electrolytes depends upon prompt recognition and treatment of the underlying disease, and early therapy to cover obligatory expenditure and undue losses.

Excessive losses require replacement regardless of the age or maturity of the infant. However, we have interpreted the available data to indicate that the requirements for obligatory expenditure of premature infants differ from those of full term infants for the age period 0 to 3 days. After 24 hours of life premature infants require sufficient fluid, electrolytes and calories to provide for basal needs, whereas the basal needs of full term infants are almost negligible in the first 2 to 3 days of life. The requirements of premature infants may be calculated in the same manner as that used for full term infants after the first three to four days of life.

The success of any regimen will depend to a large extent upon the constant observation of the clinical condition and careful correlation with laboratory studies, with resultant modifications according to individual needs.

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2600 North Lawrence Street
Philadelphia 33, Pennsylvania

HYPERNATREMIC DEHYDRATION

HAROLD E. HARRISON, M.D.

LAURENCE FINBERG, M.D.

Early recognition of the hypernatremic* state is of great importance in the treatment of this problem, since delay in treatment may lead to an irreversible state resulting in either death or severe brain damage with permanent sequelae. Knowledge of the factors which may predispose to hypernatremic dehydration is of value in the diagnosis, and, perhaps of even more importance, can lead to recommendations for the prevention of this disturbance.

PREDISPOSING FACTORS IN GENESIS OF HYPERNATREMIC DEHYDRATION

Early Infancy and Prematurity

The relatively large evaporative water losses per kilogram of body weight of this group of infants, and the inefficiency of renal conservation of water due to renal immaturity, explain their susceptibility to hypernatremia.[7]

Interference with Oral Intake of Water

This may occur as a result of the anorexia or nausea and vomiting of acute infections. Reduced intake may also be due to neglect of water administration to infants. A special group of hypernatremic patients is accounted for almost solely by this mechanism, namely, those with cerebral defect who either have insufficient access to water or whose

From the Pediatric Division, Baltimore City Hospital, and the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

* We have classified patients as hypernatremic if serum sodium concentrations are 150 mEq. per liter or higher.

cerebral impairment leads to a lack of thirst response in the presence of the usual stimuli.[10] Clinically these patients have to be distinguished from those whose brain damage is secondary to hypernatremic dehydration. At times this distinction may be difficult.

Excessive Losses of Electrolyte-Free Water because of Increased Evaporative Water Loss through Skin and Lungs

This is seen in febrile states, environmental heat stress, and in salicylism and other causes of hyperventilation.[8] Profuse sweating may also contribute, since normal sweat has a concentration of sodium only 10 to 35 per cent that of extracellular water.

Excessive Losses of Water in Stools

The concentration of sodium in the water of normal stools and often in diarrheal stools is considerably less than that in extracellular fluid.[9] However, there is great variation in the concentration of sodium in the water of diarrheal stools, and we have not been able to demonstrate any good correlation between the concentration of sodium in stool water and the development of hypernatremia. This factor, then, appears highly variable in etiologic significance, since no significant difference can be found between the concentrations of sodium in stool water of hypernatremic patients and normonatremic patients who have a similar degree of water loss due to diarrhea. Probably the volume of water lost in the stools is the important factor.

Excessive Administration of Solute (Electrolyte and/or Protein) to Sick Infants[1]

An infant who is being subjected to a dehydrating influence, be it diarrheal disease, anorexia or fever, has a smaller margin of safety for water conservation. The intake of high protein and electrolyte feedings, or large volumes of saline solutions, orally or parenterally, increase the renal water requirement obligatory for excretion of excess electrolyte and urea. This water may have been easily spared in health, but its loss now serves to increase water deficit. The feeding of undiluted and unmodified cow's milk to a two-month-old infant is an example of a high solute load which is easily tolerated by a well infant, but may cause water deficit in a sick infant.[7] In infants with diarrhea the total quantity of sodium intake is important as well as the concentration of sodium in the solution. Even though a fairly dilute electrolyte solution (50 mEq. per liter of sodium) is given orally to infants with diarrhea, hypernatremia may result if it is given in unphysiologically large quantities.[1] Such patients have been noted to produce copious watery stools which

are apparently very dilute in sodium. Only a few actual measurements are available on these infants, but no other explanation is at hand except that of large losses of water in the stool.

Salt Poisoning, Either Inadvertently by Addition of Salt to Feedings, or Iatrogenically by Injudicious Therapy, so that Excessive Amounts of Sodium Salts Are Given to Dehydrated Infants[3, 4, 9]

Excessive intake of salt produces an increased body sodium content, and because of attendant anorexia or vomiting plus the usual evaporative water losses there may be dehydration as well.

Excessive Renal Water Loss as in Diabetes Insipidus and "Nephrogenic" Diabetes Insipidus

Any interference with the necessary large water intake of these patients quickly leads to hypernatremic dehydration.

PHYSIOLOGY AND PATHOLOGY OF HYPERNATREMIA

Hypernatremia can be associated with an increased total sodium content of the extracellular fluid as in patients given excessive amounts of salt. In subjects with severe water deficit, however, total extracellular sodium is reduced despite high concentrations of sodium because of reduction of extracellular fluid volume. All patients with hypernatremia show certain manifestations which are thought to be the result of intracellular dehydration secondary to the increased osmotic concentration of extracellular water.

During experimental hypernatremia the muscle cells take up sodium, as well as lose water. In addition they reach osmotic equilibrium by apparent dissociation of intracellular complex particles into smaller units. This latter reaction appears to occur to a much greater extent in brain cells, where little or no sodium enters.[5] This special behavior of brain cells possibly accounts for the severe functional central nervous system changes seen in hypernatremia.

Intracranial bleeding occurs at times in hypernatremic patients and also in animals made acutely hypernatremic. This is apparently the result of injury or rupture of capillaries and venules secondary to reduction in cerebrospinal fluid pressure.[3, 5, 6] Subdural effusions have also been encountered.[3] These phenomena are probably not responsible for the common symptoms and signs of this disorder, but may in occasional instances cause death or severe residual damage.[3, 4, 5, 9]

The composition of the extracellular fluid may show other derangements because of the underlying disease, and such secondary phenomena as metabolic acidosis and the biochemical changes of renal insufficiency are seen in addition to the effects of the hypernatremia itself. The most

important of the biochemical disorders secondary to hypernatremia are changes in concentration of potassium and calcium. Potassium deficits are often large in these patients because of losses in gastrointestinal secretions and in the urine. At times the serum potassium concentration will be low in the face of evidences of renal insufficiency;[4] this phenomenon may represent an extrarenal adjustment to hypernatremia as well as being a reflection of a reduced body potassium content. If renal impairment persists, serum potassium levels, of course, will rise.

Serum calcium levels are frequently reduced in hypernatremic patients. The equilibrium of this ion is affected by multiple factors, but it seems probable from studies in patients and experimental animals that the calcium level is in some way altered by hypernatremia, particularly if associated with potassium deficiency.[3, 4] In addition, acute renal insufficiency leads to phosphate retention, which may play a contributing role. The metabolic acidosis present in some patients may protect against overt tetany, but when the acidosis is corrected before correcting the hypernatremia, hypocalcemic tetany may occur, as may occasionally be true in untreated hypernatremic dehydration if acidosis is minimal or absent.

CLINICAL RECOGNITION OF HYPERNATREMIC STATES

This topic is of paramount importance in any discussion of therapy, since in many situations there is a considerable time lag in obtaining chemical data from the laboratory. The condition can be deceptive because the dehydration, though marked, may seem inapparent to one looking for signs of classic dehydration.

The first step toward recognition of hypernatremic dehydration begins with the history of the etiologically disposing factors discussed above. An objective criterion is loss of 10 to 15 per cent of the body weight without the signs of classic dehydration such as loss of skin elasticity and turgor, or circulatory impairment. The hypernatremic patient may have lost 10 per cent of his body weight without evidence of circulatory embarrassment and look deceptively well for a time. These infants are often extremely thirsty, and this is one of the reasons why excessively large intakes of sodium may result if they are given electrolyte solutions *ad lib*. As they become sicker, however, nausea and vomiting limit the fluid intake. Fever is commonly associated with hypernatremia, so that it may be both a predisposing factor and a manifestation of this state.

The presence of signs and symptoms referable to the nervous system has been most important in the diagnosis. Disturbances in consciousness ranging from lethargy to coma have been common. Hyperirritability to stimuli despite extreme lethargy when undisturbed has been characteristic. Other signs such as tremors, exaggerated deep tendon reflexes and

muscle rigidity, including nuchal rigidity, have been common, and occasionally convulsions are seen. The concentration of protein in the cerebrospinal fluid is usually elevated.[5]

Hypernatremic dehydration when extreme may also be accompanied by reduction in extracellular fluid volume, with the associated circulatory disturbances. Such a "mixed" clinical picture is difficult or impossible to diagnose by clinical criteria alone, and in such instances the laboratory remains the *sine qua non* of diagnosis. However, this latter type of patient has a greater sodium deficit than the group previously described, so that administration of solutions with the usual concentrations of sodium salts given to dehydrated patients would not be so harmful as in the more common form of hypernatremia.

TREATMENT

The goal of treatment is not the rapid restoration of serum sodium levels to normal, but rather the safe return of the patient to optimum physiologic balance without undue risk of complications. Experience in the treatment of hypernatremic subjects has indicated that administration of water rapidly in large quantities in an effort to bring the sodium concentration into the normal range is dangerous. Such an approach may precipitate a severe convulsive state. It has been pointed out that certain adjustments of brain cells to the increased extracellular sodium concentration have occurred, and rapid reduction of extracellular sodium evidently precipitates another disturbance of equilibrium. Since these patients are usually not in circulatory collapse, the pressure for rapid replacement of fluid volume is removed, and the rehydration process may safely be carried out gradually. It is important, however, that fluid administration be started promptly when the diagnosis is suspected and that it be continued at the proper rate.

The composition of the fluid to be administered should, of course, be hypotonic with respect to sodium and chloride. Theoretically, it might be possible to eliminate these ions completely and give electrolyte-free glucose water. This has two drawbacks: first, many patients do have some extracellular electrolyte deficits, and, secondly, the addition of some sodium makes slightly more rapid administration of fluids possible and safe. Concentrations of sodium above 40 mEq. per liter have been found to be excessive for these patients. Current information suggests that sodium concentrations of 15 to 20 mEq. are the most suitable. Since most patients have a greater deficit of sodium than of chloride (metabolic acidosis), it is customary in our clinic to use 1 part of sixth-molar sodium lactate to 2 parts of 0.85 per cent saline solution in preparing the sodium-containing portion of the solution. The desired concentration indicated above may be reached by combining 1 part of sixth-

molar sodium lactate, 2 parts of 0.85 per cent sodium chloride and 21 parts of 5 per cent glucose in water. If the acidosis is severe (indicated by carbon dioxide contents of less than 8 mEq. per liter), sixth-molar sodium lactate may be used in place of the saline, and thus 3 parts of sixth-molar sodium lactate and 21 parts of 5 per cent glucose in distilled water are given. (Final concentration of sodium lactate is M/48.) Solutions such as these should be given intravenously. The rate of administration to an infant should be such that 200 ml. per kilogram are given during the first 24 hours (0.14 ml. per kilogram per minute). This provides for the deficit of water of about 10 to 15 per cent of the body weight as well as for the continued water requirements of 70 to 100 ml. per kilogram per day for infants.

Fluid therapy for the second and subsequent days can be reassessed daily. If tolerated, glucose water may be given orally together with the appropriate electrolyte by the end of 12 to 24 hours or even earlier in milder cases. Although potassium deficits may be severe, it is wise to withhold administration of potassium initially, since many of these patients are oliguric or temporarily anuric. Once it is apparent that urinary output is adequate, potassium replacement should be started. The oral route is preferable when feasible, and 3 to 5 mEq. per kilogram per day are advised initially (10 per cent potassium citrate solution provides 1 mEq. of potassium per milliliter and can be given orally diluted with fruit juice or other fluid). If the parenteral route is necessary, the usual precautions for parenteral potassium administration should be carefully followed. The concentration of potassium chloride in the solution given intravenously should not exceed 20 mEq. per liter (0.15 per cent potassium chloride).

A daily weight is important in assessing the previous day's fluid replacement. It is common for these patients to show evidences of overexpanded extracellular fluid with visible edema even before they are completely rehydrated because of the lag in intracellular uptake of water.

Part of the therapy should be directed to controlling nervous system complications. Should convulsions occur, the usual anticonvulsant drugs are indicated. We have used subcutaneous phenobarbital sodium and rectal paraldehyde as agents which seem particularly safe in infants. The dose of phenobarbital sodium used is 5 mg. per kilogram repeated once in 20 minutes if necessary. Subsequent maintenance phenobarbital therapy is continued as in any acute convulsive state. When paraldehyde is required to control convulsions, 2 to 4 ml. are given rectally with an equal volume of cottonseed oil. If instilled through a small catheter and the buttocks taped tightly together with adhesive, the paraldehyde is usually retained. It is disconcerting to have nervous system manifestations develop while the patient is receiving therapy, but present knowledge indicates that this occurrence may be inevitable after a certain

amount of damage has occurred during the hypernatremic phase. Thus some nervous system damage may be irreversible before convulsions occur.

Subdural effusions may be suspected and diagnosed by needle aspiration. Our experience to date has not shown any improvement in these patients from paracentesis or surgical drainage of subdural effusions over simple expectant watching. It would seem wise, until better criteria are established, to regard and assess each case individually. Intracranial bleeding may occur in several different sites, and here again individual consideration of treatment is indicated. Hypocalcemia may be averted or treated when present by the administration of 10 to 30 cc. of 10 per cent calcium gluconate per day in the intravenous fluids.

In summary, the treatment of hypernatremic dehydration consists in administering an appropriate fluid volume of low (15 to 20 mEq. per liter) sodium concentration at a slow rate until water deficit is overcome. At the same time attention should be paid to needs for potassium and calcium. Meanwhile the nervous system complications must be managed symptomatically. In rare instances aspiration of subdural effusion or hematoma may be indicated.

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4940 Eastern Avenue
Baltimore 24, Maryland

POSTACIDOTIC COMPLICATIONS OF DIARRHEA

DAVID CORNFELD, M.D.

Two phases of acute diarrheal illness in infants have been described—that of acidosis and dehydration, during which losses of fluid and electrolyte occur, and the postacidotic recovery period following repair of deficits of water and electrolytes. As correction of these deficits is accomplished by administration of water and electrolytes, depletion of extracellular ions ensues because of the rapid intake of these ions by soft tissue and bone. It is during the latter phase that Rapoport et al.[14] first described a syndrome characterized by sudden collapse, twitching, convulsions and respiratory arrest—all relieved by administration of calcium-containing salts. In recent years the significance of derangements in other ions (potassium and sodium) as contributory factors to this catastrophic clinical picture has become more evident. When anticipated, this complication of diarrhea can usually be prevented, and when it is recognized early and treated adequately, late sequelae may be avoided.

CLINICAL FEATURES

Predisposing Factors

Prematurity, malnutrition, severe recurrent and/or persistent diarrhea, high fever and dehydration all favor the occurrence of severe symptoms in the postacidotic recovery period.

Clinical Manifestations

The signs of postacidotic derangement may be those primarily of central nervous system or cardiorespiratory system dysfunction, or those due to diffuse visceral hemorrhage.

From the Department of Pediatrics, University of Pennsylvania School of Medicine, and the Hospital of the University of Pennsylvania, Philadelphia.

Rapoport has classified the changes in the neuromuscular function as (1) central—including lethargy, irritability, generalized hypertonicity, and convulsions of the clonic-tonic type—and (2) peripheral—including carpopedal spasm, laryngeal stridor and mechanical hyperexcitability. He attributes eye incoordination (nystagmus and strabismus), which is frequently seen, to either effect. The Chvostek sign, an aid in the diagnosis of latent tetany in babies older than one month, is of no significance in younger babies because it is a normal finding.

Changes in autonomic function are also noted: The respirations are irregular and sighing, and there are often long periods of apnea. Cardiac

TABLE 28. *Comparison of Signs and Symptoms of Postacidotic State and Hyperosmolarity*

	POSTACIDOTIC STATE	HYPEROSMOLARITY
Central nervous system	Irritability or lethargy, spasticity, convulsions, intracerebral hemorrhage	Restlessness, delirium, coma, hypertonicity, convulsions, hemorrhage
Cardiovascular system	Bradycardia, systolic murmur, occasionally tachycardia	Tachycardia
Respiratory system	Apnea, stridor—progressing to respiratory arrest	Hyperpnea; occasionally sudden respiratory arrest
Skin	Edema (nonpitting), blotchy cyanosis, occasionally flushed	Edema (nonpitting), flushed
Temperature	Moderately elevated	Elevated

embarrassment, occasionally progressing to shock, and cardiac standstill may occur, with bradycardia and a systolic murmur as frequent findings.

Skin changes include edema, which is firm and resistant to pitting, blotchy cyanosis or pallor, and more rarely a diffuse flush. The body temperature may be elevated. Finally there may be hemorrhagic manifestations as the most severe complication of the postacidotic period. These have a predilection for the central nervous system, the gastrointestinal tract and the skin. The findings may include petechiae, hematemesis, melena and massive subdural bleeding. If untreated, patients with severe signs of postacidotic ionic derangement may die from cerebral hemorrhage, respiratory standstill or cardiac arrest.

Incidence

Dodd[2] reported 55 cases of diarrhea and noted symptoms suggestive of the syndrome in 51. Flett,[7] in a group of 153 cases of severe diarrhea, found only 2 or 3 babies to have findings compatible with the diagnosis. Part of the difference in the two groups may be explained by other factors, e.g., the serum osmolarity. The occurrence of symptoms has

recently been attributed to the concurrent presence of hypocalcemia and hypertonic dehydration.[5, 6]

PATHOLOGIC PHYSIOLOGY

During diarrhea there is a considerable loss of water and electrolyte and nitrogenous substances. Sodium, chloride and bicarbonate are lost from the extracellular space, potassium from the intracellular space, calcium from the bone, and phosphate from bone and soft tissue. The acidosis of diarrhea is caused by the preferential loss of bicarbonate with cations in the stool and by the acidosis-producing effects of starvation, infection, cellular destruction and renal impairment. Replenishment of tissue cells during the recovery phase may lead to temporary depletion of electrolytes in the plasma. During this period a syndrome characterized by neuromuscular irritability and other symptoms has been observed. The neuromuscular irritability due to ionic changes can be crudely characterized by the following equation.[11]

$$\text{Neuromuscular irritability} \propto \frac{(Na^{+}) + (K^{+})}{(Ca^{++}) + (Mg^{++}) + (H^{+})}$$

Because of certain similarities between this syndrome and hypocalcemic tetany in infants, and the accompanying low calcium concentrations in many of the babies recovering from the acidosis of diarrhea, the manifestations of neuromuscular irritability have been attributed to the low serum calcium ion concentration.[2, 3, 13] During the acidosis of diarrhea large amounts of calcium are mobilized from the bone bank (where 99 per cent of the body calcium is stored).[1] The serum calcium level is maintained relatively constant by increased renal calcium excretion, which, together with reduced intestinal absorption, results in a negative calcium balance. With recovery there is rapid deposition of calcium and phosphorus in the bone, and lowering of the serum calcium occurs unless the calcium is replaced. In sharp contrast to hypocalcemic tetany, there is no one serum calcium level below which tetany develops and no close quantitative relationship between the extent of hypocalcemia and the clinical symptoms. However, *sudden changes* in the calcium ion concentration seem more likely to produce the symptoms than slow changes.

It has therefore been suggested[6] that the discrepancy in frequency of tetany between Flett's and Rapoport's cases might be related to the fact that the former generally used smaller amounts of alkalizing agents in treatment of diarrhea, and therefore effected slower repair of acidosis.[7] That this is not the entire answer can be adduced from the fact that in the original series of cases alkalosis was only rarely seen. Experi-

mentally, when alkalosis can be induced in normal controls even to the point of developing tetany, there is no lowering of the calcium ion concentration.[13]

Finberg,[6] more recently, has related the difference in incidence of symptoms in the two series to differences in serum sodium concentra-

TABLE 29. *Calcium Therapy in Infant Diarrhea*

INDICATIONS		
Severe diarrhea accompanied by hyperosmolarity; chronic diarrhea; diarrhea in premature; presence of symptoms and signs of postacidotic state		
ROUTES OF THERAPY		
	Intravenous	**Oral**
Preparations	Calcium gluconate	Calcium chloride Calcium lactate Calcium gluconate
Dosages	1 gm. of calcium gluconate as 2% solution, or 10% solution — every 8–12 hours if necessary	3 gm. daily for 2 days as 1% solution in formula or oral electrolyte solution (½ dosage in prematures) 4–6 gm. daily as 2% solution in formula or oral electrolyte mixture
Precautions	1. 10% solution to be given at rate no faster than 1 cc./minute 2. Observe heart rate; discontinue injection if pulse falls below 70 3. Close observation for bradycardia when given to digitalized patient 4. Do not add to phosphate - containing solution	Observe for systemic acidosis
Toxicity	1. Heart block 2. Tissue necrosis at site of injection if there is extravenous extravasation	Nausea, anorexia, hematemesis, hemorrhagic gastritis

tion rather than to the pH, noting that, in general, Rapoport's cases received more sodium-containing solutions than those of Flett. He described a partial inverse relationship between the sodium and calcium concentrations in hypertonic babies, but no correlation when the sodium concentration was less than 150 mEq. per liter. Hypocalcemia was seen in a small group of these hypertonic babies with increased plasma bicarbonate level as well as in a larger group of acidotic children. In a

group of 65 babies with normal or low serum sodium concentrations the calcium was less than 9 mg. per 100 ml. in only three; it was less than 9 mg. per 100 ml. in 28 of 38 babies with serum sodium concentrations greater than 150 mEq. per liter. Many of the symptoms noted in hypertonic children without hypocalcemia were analogous to those reported in the initial series of Rapoport (and part of the symptomatology in his babies might have been due to hyperosmolarity [Table 29]).

Since not all hypertonic babies are necessarily hypocalcemic, studies were undertaken in rats[5] to define other factors which might influence the equilibrium between the skeletal and extracellular calcium ion concentration. An increase in body sodium concentration regularly produced a temporary decrease in the calcium ion if there was a concomitant potassium deficiency. Neither an excess of sodium nor a decrease of potassium independently would produce the decrease in serum calcium ion concentration. This suggests the possibility that a sudden increase in the concentration of sodium ion on the surface of bone crystals, in the presence of a decreased potassium concentration, might interfere with the calcium ion homeostasis.

The role of the potassium ion is difficult to explain. Evidence from metabolic experiments on rat liver indicates an important relationship between calcium and potassium ions.[9] In these studies the presence of adequate calcium ion was noted to be necessary for liver slices to regain potassium ion from a low potassium ion environment. Re-establishment of the cell wall is the first step in tissue repair. This repair process requires potassium, and this in turn requires calcium ion and oxygen.

Clinical confirmation of the importance of changes in the potassium ion concentration in the picture of tetany can be found in experimental observations on human beings treated with potassium ion exchange resins[8] and low sodium intakes. Acidosis produced in these patients was corrected with sodium salts. Potassium salts were then given to repair the intracellular potassium deficits caused by the resin therapy. When the potassium-containing solution was first started, tetany frequently occurred. Apparently at this stage the cells were abnormally sensitive to small increments in the extracellular potassium level. It seems probable that a slight change in intracellular composition (increase in cell sodium) accounted for an increase in nerve fiber excitability and that extracellular changes ordinarily too small to produce tetany (a rise in potassium ion concentration from a lower level) might then have done so. In these patients edema generally preceded the onset of tetany, and symptoms occurred even in the absence of alkalosis. Treatment of the tetany required that potassium be restored even though this might temporarily aggravate the disorder.

Consideration of the foregoing data would lead one to recommend caution over too enthusiastic treatment of hypokalemia under circumstances in which there might also be hypocalcemia, as in the recovery phase of the acidosis of diarrhea. In this situation simultaneous administration of potassium and calcium salts can help to prevent the occurrence of symptoms of the postacidotic state.

TREATMENT OF POSTACIDOTIC STATE

The basic principles for the treatment of diarrhea are discussed on page 99*ff.* in this symposium. They include (1) immediate treatment for shock to restore circulation and renal function; (2) replacement of pre-

existing deficits of water and electrolyte and provision of adequate water and electrolyte for maintenance of ionic equilibrium and correction of abnormal metabolic reactions; (3) a period of starvation followed by slow resumption of oral feedings; (4) specific antibiotic therapy when the diagnosis of an enteric infection is suspected (after appropriate diagnostic tests have been performed).

Since excessive electrolyte administration, with a tendency to edema formation, may be one of the precipitating or aggravating factors in the development of hypocalcemia, electrolyte solutions must be administered with care. When hypertonicity is suspected on a clinical basis, only fluids with a concentration of sodium less than 40 mEq. per liter should be given. In addition, in small babies and prematures proportionately greater quantities of electrolyte-free solutions should be used than in older babies. The estimation of requirements (discussed in detail on page 29*ff.*) is based on clinical judgment, taking into account the history and etiology, with the help of frequent plasma chemistries. Simultaneous determinations of carbon dioxide and chloride, which account for 85 per cent of the anions, are a good indication of the total electrolyte concentration of the plasma, except when there is severe ketonemia. The nonprotein nitrogen (if there is no concomitant renal disease) is an index of water available for renal excretion; its degree of elevation a rough measure of the requirements for sodium-free solutions.

Acidosis should be corrected slowly with alkalizing agents. A convenient formula for calculating the sodium-containing solutions required to restore the bicarbonate level toward normal is as follows:

$$(27 - [HCO_3]\ \text{mEq./L.}) \times 0.3\ \text{weight (kg.)} = \text{mEq. (Na)}$$

required to raise the bicarbonate concentration to approximately 27 mEq. per liter. This formula will allow for restoration of bicarbonate in the extracellular fluid and the decrease in the extracellular volume as hydration occurs (but does not take into consideration the fact that variable amounts of sodium may enter the cells in the repair process).

When hypertonic dehydration is present, in chronic diarrhea, in prematures, or when there are symptoms suggestive of the postacidotic state, calcium-containing salts should be given. Depending on the severity of the symptoms, calcium may or may not be required intravenously. If it is, 1 gm. of calcium gluconate in a 2 per cent solution can be given by slow intravenous drip, or an alternative method is to give 10 per cent calcium gluconate at a rate no faster than 1 cc. per minute. Careful evaluation of the patient is essential during the course of the injection. An observer should listen constantly to the heart with a stethoscope in place on the chest wall during the infusion, and the

drug should be discontinued at the first sign of bradycardia or as soon as the desired clinical effect is obtained. Although rarely necessary, the initial dose may be repeated every 8 to 12 hours intravenously. Special caution is necessary when a patient is digitalized, since calcium may potentiate digitalis effect on the myocardium. Complications of intravenous therapy, in addition to the acute cardiac effects, include necrotizing lesions at the site of injection, especially if there is extravasation of the calcium-containing solution outside the vein. A further caution to be noted is that calcium salts cannot be added to phosphate-containing solutions because an insoluble calcium phosphate precipitate is formed.

Once the baby has been started on oral feedings he may also be started on oral calcium preparations available as (1) calcium chloride, $Ca\ Cl_2$—$2H_2O$, U.S.P., containing 27 per cent calcium by weight; (2) calcium gluconate, $(CH_2OH\ (CHOH)_4\ COO)_2\ Ca \cdot H_2O$, U.S.P., containing 9 per cent calcium by weight; (3) calcium lactate, $(CH_3\ CHOH\ COO)_2\ Ca \cdot 5\ H_2O$, N.F., containing 13 per cent calcium by weight. The acid reaction of calcium chloride favors calcium ion absorption. However, because it is bitter and frequently nauseating, it should be given in dilute form in the formula (or in oral electrolyte solution) at a 1 per cent concentration. The dose for calcium chloride is 1.5 to 3 gm. daily for 2 or 3 days. In prematures or in babies less than one month of age approximately half this dose may be given. When calcium chloride is not tolerated orally, the baby should be given calcium gluconate or calcium lactate in a dose of 4 to 6 gm. daily. The same dosage may be used when treatment is necessary for more than two to three days, because continuous therapy with calcium chloride may lead to systemic acidosis. Further complications of oral administration include vomiting, nausea and occasionally hematemesis (due to a hemorrhagic gastritis).

Since a deficit in potassium ion is probably important in the pathogenesis of the postacidotic state, potassium salts should be given in the repair fluids. However, in the treatment of any severe diarrhea with potassium-containing solutions, caution must be observed in that sudden, rapid correction of a low potassium concentration in the presence of a low or borderline calcium ion concentration may precipitate clinical tetany.[4] When both potassium and calcium ion concentrations are decreased, potassium- and calcium-containing solutions should be administered simultaneously. In general it is easier to correct the low potassium ion concentration than the low calcium ion concentration. Methods of administration of potassium-containing solutions are discussed elsewhere in this symposium.

Finally, specific antibiotic therapy for diarrhea should be given if an enteric infection is found.

SUMMARY

1. In the recovery phase following the acidosis of diarrhea a syndrome has been described characterized by convulsions, cardiorespiratory dysfunction, a hemorrhagic diathesis, and edema.

2. Hyperosmolarity in association with hypocalcemia and hypokalemia plays an important role in the pathogenesis of the syndrome.

3. The rationale and methods of treatment of this complication of diarrhea are described.

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3400 Spruce Street
Philadelphia 4, Pennsylvania

FLUID THERAPY IN ADRENOCORTICAL FAILURE

ALFRED M. BONGIOVANNI, M.D.

The occurrence of shock attributable to adrenocortical failure in a child is one of the most critical medical emergencies to confront the pediatrician. Proper recognition of the condition, evaluation of the various causes, and immediate treatment are mandatory. Adequate therapy consists in the administration not only of suitable parenteral fluids, but also of specific drugs. This monograph purports to detail these various aspects of the problem.

GENERAL PRINCIPLES

An excellent general review of adrenocortical metabolism in early life has been written by Gardner.[2] The adrenal cortex produces a variety of steroidal hormones, including aldosterone (mineralocorticoid), hydrocortisone (compound F), androgens and estrogens. A deficiency of the first two types of compound, particularly aldosterone, induces the clinical state pertinent to this discussion—the others play an insignificant role in the maintenance of fluid and mineral balance. Although aldosterone is the most important, hydrocortisone is not devoid of action in salt and water metabolism. As a rule, a deficiency of one of these two important substances in adrenocortical disease is accompanied by a lack of the other. The additional role of hydrocortisone in gluconeogenesis also has a bearing on the problem of adrenocortical insufficiency, since hypoglycemia is to be reckoned with in the absence of this steroid.

A defect in electrolyte regulation is a most important consequence of the lack of aldosterone. There is a tendency to sodium (and water)

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depletion and an elevation of the serum potassium. The intensity of the clinical disorder which ensues is influenced by the degree of hormonal inadequacy. The picture is also varied by the rapidity with which adrenocortical failure occurs. Chronic adrenocortical failure of the classic Addisonian variety is rare in pediatric practice.

EVIDENCE OF ADRENOCORTICAL INSUFFICIENCY

Adrenocortical failure in infancy and childhood is more often unaccompanied by the many premonitory signs and symptoms to be found in adults with Addison's disease. In children there may be anorexia, nausea, emesis, diarrhea and rapid weight loss with dehydration and shock. Such manifestations are usual in several other diseases of children which are not induced by primary adrenocortical disease. Hence a searching wariness is in order, as well as temperance, to avoid assigning a vast number of other disturbances to the category of adrenocortical deficiency, with the wide-scale improper application of the measures to be described herein.

The usual laboratory findings of adrenocortical failure are as follows: decreased serum sodium and chloride; increased serum potassium and nonprotein nitrogen; hemoconcentration. An increase in circulating lymphocytes and eosinophilis may also occur. The small heart size, abnormalities of the electrocardiogram and the flat glucose tolerance curve do not lend themselves well as emergency diagnostic tools. The more specific applicable endocrinologic tests, previously reviewed in these pages and elsewhere,[10, 12] are best conducted to establish a correct diagnosis, but treatment must usually be instituted quickly; hence the more accessible and indirect criteria already mentioned take precedence. Nevertheless the most useful endocrinologic tests should be mentioned: the serum and/or urine corticoids. The 17-ketosteroids are generally not helpful in the diagnosis of insufficiency in childhood. The determination of aldosterone is highly specialized at present, and the diagnosis of adrenocortical insufficiency must be made without this test, except in the rare instance of a pure aldosterone deficiency.[4] It is important to mention at this point that in "adrenal crisis" of extremely sudden onset the serum electrolytes may be normal on first examination.

CAUSES IN CHILDHOOD[3, 13]

Primary Aplasia in Infancy. This is often accompanied by other congenital abnormalities, especially anencephaly. These conditions are usually incompatible with life. Hypoplasia of the adrenal, with a longer period of survival, has also been described.[3]

ADRENAL HEMORRHAGE IN THE NEWBORN is probably due to traumatic delivery. The symptoms of adrenocortical insufficiency occur early in life and are indistinguishable from those of overwhelming septicemia. Immediate recognition and vigorous treatment are required, and often the condition is fatal. Certainty of such a diagnosis in an infant who survives is difficult, although calcification of the adrenal glands may be visible by x-ray examination in later life.

TEMPORARY HYPOFUNCTION OF EARLY LIFE. Jaudon,[5, 6] in particular, and others have called attention to a syndrome in young infants characterized by failure to thrive, emesis, dehydration and collapse with excessive renal loss of salt and water. This can be corrected by therapy

TABLE 30. *Acute Adrenocortical Insufficiency in Childhood*

Newborn infant	Primary aplasia (other malformations) or hypoplasia
	Adrenal hemorrhage (traumatic birth, breech)
	Fulminating infections
	Congenital virilizing adrenocortical hyperplasia
	Transient (rare)
Sudden withdrawal of corticoid therapy	Acute stress during corticoid therapy and negligent discontinuation
Acute illness	Fulminating infection (Waterhouse-Friderichsen syndrome)
	Surgery with Addison's disease (or other acute stress)
	Surgery on patients with adrenogenital syndrome (or other stress)
Sudden acute adrenocortical failure due to unknown causes	

with suitable adrenocortical hormones and salt. Eventually treatment was discontinued in those infants described in the literature. Such a syndrome is believed to be rare, and in this Clinic only one case has been seen conforming to the stated criteria, although detailed study of the urinary steroids revealed evidences of normal adrenocortical function in spite of a satisfactory response to "specific treatment." Hence a definite adrenal lesion need not be responsible. The indiscriminate treatment of numerous infants presumed to have this condition, such as has been promulgated from time to time, is not endorsed by this writer.

FULMINATING INFECTIONS may be accompanied by signs of adrenocortical deficiency as in the Waterhouse-Friderichsen syndrome. The mortality rate is high, and postmortem examinations often reveal damage to the adrenal cortex. It is uncertain whether the entire responsibility for this serious illness rests upon the adrenal cortex alone—the toxic effects of the infection per se are no doubt also culpable. Although suitable therapy as described herein may be advisable, and

fashion practically demands this, a recent well controlled study failed to indicate the advantage of treatment with adrenal steroids.[8]

Congenital Virilizing Adrenocortical Hyperplasia. About one fourth of patients with the adrenogenital syndrome due to adrenocortical hyperplasia suffer from an electrolyte disturbance such as might be attributed to a deficiency of mineralocorticoid.[13] Although the reasons for this are not entirely clear, there is evidence that the cause is one of degree of severity in the enzymatic defects described elsewhere.[1] The affected infant usually fails to thrive and suffers emesis, dehydration and shock in early life. Less often these symptoms are deferred until a later age and occur under the stress of acute infections. The condition is readily suspected in a female pseudohermaphrodite with these symptoms, but the male at times escapes proper recognition. The urinary 17-ketosteroids and pregnanetriol are abnormally elevated in this disorder. Early and vigorous treatment is required.

Discontinuance of Steroids. The sudden withdrawal of adrenocortical steroids for therapy other than primary adrenal disease may be followed by the manifestations of adrenal failure discussed earlier. It must be recalled that the adrenal cortex atrophies during the long-term use of various steroids and only gradually recovers. Parents must be warned against this possibility. An infant was admitted to this Clinic in collapse 24 hours after negligent cessation of prolonged cortisone treatment for an allergic disorder. A second child receiving steroid therapy under supervision died during an emergency appendectomy in another institution after many hours had elapsed since the last dose of oral cortisone.

Acute "Adrenal Crisis" *may follow unilateral adrenalectomy* for a tumor causing Cushing's syndrome, since the contralateral gland is usually atrophic. Bilateral adrenalectomy is obviously an occasion for the anticipation of adrenal insufficiency; hence the preparation of the child must be suitable.

Exhaustion. Rarely children submitted to prolonged nonspecific illnesses, such as those requiring repetitive surgery, will exhibit the usual adrenocortical responses, only to lapse into crisis later. This explanation is not an invitation to apply the measures described in every such instance. When such children succumb to their malady, we have at times noted adrenal hemorrhage at postmortem examination. This may be attributable to what we have termed "superstress" with adrenal damage secondary to profound adrenocorticotropic stimulation. Such an event is also known to accompany extensive burns.

Addison's Disease. Adrenal crisis may occur with chronic adrenal insufficiency. Generally the condition may be recognized by various signs and symptoms before the occurrence of frank crisis. The appearance of dehydration and shock may be due to inadequate treatment or

may be precipitated by acute infections or injuries. As stated earlier, this form of adrenal cortical insufficiency is uncommon in childhood.

FLUID THERAPY

In the absence of the adrenocortical mineralocorticoid (aldosterone) there is a loss of extracellular water and sodium into the urine, the intracellular compartment and possibly bone. Some loss may occur via the sweat. With a diminution of the extracellular fluid volume, there is extracellular dehydration, hypotension and shock. On the other hand, there is potassium retention with somatic and cardiac muscle weakness. The hormone designated as the mineralocorticoid promotes the renal tubular reabsorption of sodium and diminishes the reabsorption of potassium. The glomerular filtrate contains a concentration of sodium, potassium and chloride which is similar to that in the serum. The mineralocorticoid produces a diminution in urinary sodium and augmentation of potassium, while in its absence there follows an undue loss of sodium (and chloride) and a retention of potassium. It is also true, however, that there are transfers of sodium and potassium across other cellular membranes under the influence of the mineralocorticoid, so that the alterations in the serum sodium and potassium are accompanied by inverse changes in the intracellular fluid compartment. Thus the loss of serum sodium and water is not entirely limited to an extracorporeal one, in the absence of the mineralocorticoid—there is some "loss" into the intracellular area. This means that the degree of extracellular dehydration may be considerably greater than that ordinarily estimated by the loss of total body weight. It also implies that during the treatment of adrenocortical insufficiency replacement with specific hormones will bring about appropriate shifts of fluid and electrolyte between the extracellular and intracellular compartments, with partial restoration of those deficiencies apparent from the study of the serum alone. Extracorporeal losses require further replacement, but the needs for parenteral replacement must not be based on assumptions which neglect the former considerations.[11] The deficiencies of sodium and water are primarily extracellular, and the losses are attributable to diversion into intracellular as well as renal (urinary) areas.

These realizations indicate that isotonic saline solution (in 5 or 10 per cent glucose) satisfies the needs. Supplementary potassium as an immediate measure is contraindicated in adrenocortical insufficiency unless hypopotassemia develops later as a consequence of excessive treatment with adrenal steroids.

Early therapy should consist in the intravenous administration of fluids, and in many instances oral treatment may be instituted within 24 to 48 hours. Although the fluid requirements will be given first, the

other supportive measures are equally important and must be initiated simultaneously. The estimated losses per kilogram of body weight for a child in "adrenal crisis" have been described by Talbot[11] as follows: water, 50 ml.; sodium, 10 mEq.; chloride, 8 mEq.; potassium, 0 or retention. The loss of fluid from the body is less than would obtain in a child with equally severe dehydration and normal adrenocortical function. Under the latter circumstances there is loss of intracellular and extracellular water, whereas in the face of adrenocortical insufficiency it is primarily extracellular water which escapes (some into the intracellular compartment).

Early fluid replacement is essential, and the estimates recommended are those which ordinarily fulfill the needs for replacement and maintenance during the first 24 hours, provided the other measures (described below) are also used. Thus the virtually simultaneous administration of adrenocortical hormones should halt progression of the defects, and the continuous derangement of the electrolytes and fluid are assumed to have been arrested. For reasons amplified earlier, the volumes of parenteral fluids may appear to be modest when compared to those advised for other types of dehydration. Infants weighing up to 7.5 kg. should receive 120 ml. per kilogram of isotonic saline solution in 10 per cent glucose. Approximately 100 ml. per kilogram should be given for those weighing between 8.0 and 16.0 kg., and 75 ml. per kilogram when the weight is 20 kg. or greater. These figures consider the differences in extracellular volume for age and size. When there is extremely severe shock, 5.0 ml. of plasma per kilogram of body weight may be substituted as part of the replacement fluid, but the author does not believe this to be generally necessary. The rates of flow should be adjusted so that the total requirement is available during the first 24-hour period, although 20 to 25 per cent of the total may be delivered, with care, during the first two hours. After the first day the maintenance needs are about one third to one half those stated, given now as half-isotonic saline solution in 5 per cent glucose, but it is unwise to rely on a more precise dictum, since variable responses to the other supportive measures may alter the needs, and the pediatrician must be guided by the clinical status of the child and the daily determination of the serum electrolytes. The use of morphine is contraindicated. When oral treatment is feasible, ordinary fluids may be allowed as tolerated with additional sodium chloride (1.0 gm. per each 10 kg. of body weight) added to the milk or as enteric-coated tablets.

The need for diligent supervision and individuality of management cannot be overemphasized. Thus the requirements for repair and maintenance may exceed the recommendation in infants with the salt-losing form of the adrenogenital syndrome. The administration of adreno-

cortical hormones, discussed below, will diminish the needs for water and electrolytes.

Adrenal Hormones

It is advisable to administer soluble hydrocortisone hemisuccinate (Solucortef, Upjohn) by vein, at once, approximately 1.5 to 2.0 mg. per kilogram (as hydrocortisone equivalent). As soon after as possible, hydrocortisone should be administered intramuscularly, 2.0 mg. per kilogram, and repeated daily for 3 or 4 days, thereafter altering the dose, depending upon the clinical condition and the progress of the

TABLE 31. *Treatment of Adrenal Crisis*

1. Intravenous fluid	75–120 ml. of isotonic saline in 10% glucose 5.0 ml. of plasma/kg.
2. Hydrocortisone hemisuccinate I.V. (Solu-cortef, Upjohn)	1.5 mg./kg. at once
3. Epinephrine or norepinephrine for shock	
4. DOCA in oil	2.0 mg. I.M. at once 1.0 mg./day thereafter
5. Antibiotics and other supportive treatment—NO morphine	

patient. The intramuscular therapy has a longer duration, and after the correction of shock this steroid is slowly absorbed over many hours, obviating the need for further intravenous therapy. The various other crude adrenocortical extracts previously recommended are no longer needed. The early use of hydrocortisone in large doses exerts some beneficial effect on the electrolyte disturbance, replaces the requirements for gluconeogenesis, and acts permissively in restoring the blood pressure. The newer analogues of hydrocortisone are without any advantages in the treatment of adrenocortical failure, and the "older" compounds (cortisone and hydrocortisone) are preferred.

In the early stages of treatment desoxycorticosterone acetate (DOCA) should be administered intramuscularly, as a solution in sesame oil containing 5 mg. per milliliter in a dose of 2.0 mg. on the first day and 1 to 2 mg. a day thereafter. This compound restores the electrolyte regulation and diminishes the salt requirements. In some special instances, such as the salt-losing form of the adrenogenital syndrome in infancy, as much as 5.0 to 6.0 mg. a day may be needed. This requirement diminishes, however, over a period of time, when prolonged therapy with hydrocortisone is instituted as described by Wilkins.[13] After recovery from shock, if the adrenocortical insufficiency is chronic, prolonged treatment with DOCA may be required. A long-acting preparation, desoxycorticosterone trimethylacetate (Percorten, Ciba),

containing 25 mg. per milliliter, may then be given intramuscularly every 25 to 30 days in a total dose of approximately 20 times the daily requirement of DOCA in oil. Another satisfactory preparation is the pellet for implantation, 125 mg., which releases about 0.5 mg. a day and lasts for 10 to 12 months. A sufficient number of pellets is introduced to satisfy the daily requirements of the child, as determined by the prior administration of DOCA in oil. The latter treatment is preferred in the salt-losing form of the adrenogenital syndrome, in which case—and with proper continuous hydrocortisone treatment—no further mineralocorticoid will be needed by the time the pellets are consumed.[13] Another drug, fluorohydrocortisone, may be given orally as a substitute for the previously mentioned salt-retaining compounds, in a dose of 0.1 to 0.3 mg. a day. In these quantities fluorohydrocortisone may not be relied upon for gluconeogenetic action, so that hydrocortisone or its analogues must be continued under some circumstances. Aldosterone itself is presently unavailable for routine therapy, and in any event the synthetic compounds described are effective.

It is advisable to administer a vasopressor substance at once to children in shock. Epinephrine (0.1 to 0.2 mg.) may be given intravenously and repetitively as required for shock. An alternative approach is to give norepinephrine (Levophed bitartrate, Winthrop). One milliliter of the 0.2 per cent solution, equivalent to 1.0 mg. of base, is added to 250 ml. of 5 per cent glucose solution. In this Clinic the bottle containing this mixture is connected via a **Y** tube to the system delivering the recommended intravenous electrolyte solution, and a slow rate of flow is established and maintained at a rate which will support the blood pressure. Every precaution should be taken to prevent this solution from reaching the vein in high concentration or from seeping into the subcutaneous tissues. It is important to note that in severe adrenocortical insufficiency the vasopressor drugs may be ineffective until after the administration of hydrocortisone.*

The underlying disease must of course be treated. In overwhelming infections suitable antibiotic therapy is necessary. The caloric needs and the level of the blood glucose should also be satisfied. As soon as possible, oral feedings should be permitted.

Special Considerations

Certain recommendations are necessary for the child about to undergo unilateral (or bilateral) adrenalectomy, or for the child who has been

* Another vasopressive agent, l-1-(m-hydroxyphenyl)-2-amino-l-propanol, has certain advantages over norepinephrine. Its action is smoother, and the risk from seepage into tissues is less. About 25 mg. of the bitartrate (Aramine—Sharp & Dohme) may be added to 250 ml. of 5 per cent glucose and used as above.

treated for a long time with pharmacologic doses of numerous corticoids and now requires surgery, or for the child previously maintained on suitable treatment for chronic adrenocortical insufficiency (including the adrenogenital syndrome), suddenly confronted with the stress of acute illness, injury or surgery. Of foremost importance is recognition of this dilemma. Certain children should carry on their person suitable identification cards with a warning: "I have Addison's disease," or "I am on cortisone." In this Clinic such a practice is rigidly endorsed. Children with the adrenogenital syndrome are constantly subject to the risk of acute adrenocortical insufficiency with stress.

If there has been satisfactory control of fluid and electrolyte balance up until the time of unexpected surgery (or some other unanticipated emergency), an adrenal crisis may be averted by the use of cortisone acetate, intramuscularly, 2.0 mg. per kilogram daily. It is unwise to rely upon continued oral treatment during an emergency. In addition, a total of 1.0 mg. of desoxycorticosterone acetate in oil may be used daily for 2 or 3 days. Throughout the period of stress the serum electrolytes, hematocrit and nonprotein nitrogen should be determined daily. Usually, within a few days, it is possible to return to the previous routine of control or pharmacologic therapy. On the other hand, if there is already evidence of an adrenal crisis, all the proposed measures should be used with suitable modifications to meet the specific situation. One must avoid the application of excessive fluid, salt and hormonal treatment.

Complications of Treatment

With improvement in the child's condition, it is necessary to readjust the requirements for salt, water and adrenocortical hormones. Even during the first few days, excessively enthusiastic therapy may lead to hypertension, edema, cardiac failure, hypernatremia and hypokalemia with muscle weakness. The child should be observed repeatedly for undue elevation of the blood pressure, pretibial edema and impending cardiac failure. The serum electrolytes should be determined daily, and frequent electrocardiograms are advisable as a guard against excessive therapy as well as a guide to restoration. Certain special synthetic steroids shown to antagonize aldosterone (the spirolactones) may be of value in the correction of overtreatment, but these are as yet untried in this situation.[7, 9]

Further Discussion

Many children with adrenocortical insufficiency may require only temporary support, e.g., those suffering shock following the withdrawal

of adrenocortical steroids, after a unilateral adrenalectomy, overwhelming infections, and rarely from other ill-defined causes. When the adrenocortical disorder is chronic, as in Addison's disease or the adrenogenital syndrome, suitable therapy is required indefinitely.[12, 13] It behooves the pediatrician to exert his best judgment so that errors may be avoided. Thus the commitment of the child with apparent "adrenal crisis" due to unknown causes to indefinite therapy may be unwarranted. On the other hand, as the patient recovers from the crisis, the treatment should be slowly discontinued and the adrenocortical function carefully evaluated in order to rule out chronic adrenocortical disease requiring prolonged guidance. The matter of the extended management of chronic adrenocortical insufficiency is not pertinent to the present discussion and has been described by others.[11, 12, 13] It is well to recall that certain conditions, such as diarrhea and renal disorders, may show changes in the serum electrolytes resembling acute adrenocortical insufficiency, and these may often be corrected by suitable parenteral fluids and minerals alone.

CONCLUSION

The occurrence of sudden dehydration and shock in childhood, due to adrenocortical failure, must be recognized as soon as possible and treated adequately at once. Rapid replacement of fluids and electrolytes, as well as suitable steroidal therapy, is essential. The use of vasopressor substances and specific treatment for the underlying cause are also important. Since the dehydration is primarily extracellular, repair solutions may consist of isotonic saline. Although rapid correction is essential, overtreatment must be avoided, particularly after the introduction of adrenocortical steroids. The child should be observed carefully during the recovery stage in order to discover the rate at which the various therapeutic measures may be withdrawn and to detect those signs of chronic adrenocortical insufficiency which may necessitate indefinite treatment. Indiscriminate assignment of many nonspecific diseases in childhood to the category of adrenocortical insufficiency is decried, although admittedly, in unusual circumstances, the measures described above may be helpful in conditions not attributable to primary adrenocortical disease.

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1740 Bainbridge Street
Philadelphia 46, Pennsylvania

THE ELECTROLYTE ABNORMALITY IN CYSTIC FIBROSIS OF THE PANCREAS

GIULIO J. BARBERO, M.D.

MAARTEN S. SIBINGA, M.D.

In 1951 Kessler and Anderson[26] reported the increased incidence of heat prostration in patients with cystic fibrosis. This observation led to the significant discovery by di Sant'Agnese and his co-workers[9, 11, 12] of the elevation of the sodium and chloride in the sweat of patients with cystic fibrosis of the pancreas. Many workers have confirmed their findings.[2, 3, 33, 34, 39, 43, 44, 46]

Such elevated electrolyte levels have been of great use in the diagnosis of milder cases of cystic fibrosis and those which do not resemble the classic clinical picture. As a result of the knowledge initiated by the discovery of the sweat electrolyte abnormality, the concept of cystic fibrosis of the pancreas has emerged as a familial disease with focal involvement of all the exocrine glands of the body. The principal manifestations are those resulting from pulmonary obstruction by an abnormally viscid mucus, pancreatic insufficiency and excessive sodium chloride excretion in the sweat.

This paper summarizes our present knowledge of the electrolyte disturbance in cystic fibrosis and its implication in treatment.

RESULTS OF STUDIES ON SWEAT ELECTROLYTES

Table 32 shows the ranges and means of the sweat sodium and chloride in both the control and cystic fibrosis groups reported in recent studies obtained by many different methods. The mean value of sweat sodium in 272 children free of obvious disease was 28 mEq. per liter, with a range of 1 to 120 mEq. In the 212 patients

From the Children's Hospital, Philadelphia, Pennsylvania.

TABLE 32. *Comparison of Results on Sweat Na and Cl in Normal Children and Patients with Cystic Fibrosis*

AREA OF COLLECTION	STIMULUS	METHOD OF COLLECTION	CONTROLS					PATIENTS WITH CYSTIC FIBROSIS				
			No. of Cases	Na mEq./L. Range	Na mEq./L. Mean	Cl mEq./L. Range	Cl mEq./L. Mean	No. of Cases	Na mEq./L. Range	Na mEq./L. Mean	Cl mEq./L Range	Cl mEq./L Mean
Midabdomen or scapular region[11]	32.2° C. 50% humidity	Gauze patch to midabdomen	50	10.0–120.0	59.0	4.0–80.0	32.0	43	80.0–190.0	106.0	60.0–160.0	106.0
Back[20]	Thermal	Plastic bag Gauze Blankets	33		30.5		35.3	58	70.0–200.0	119.0		130.0
	Thermal[16]	Gauze	30	5.9–7.7	27.0	Trace to 50.0	18.0	6	86.0–132.0	107.0	85.0–138.0	108.0
Body[18]	36.6° C. 60% humidity		6	11.0–35.0	18.0	10.0–35.0	16.0	9	42.0–79.0	79.0	51.0–137.0	80.0
Abdomen[23]	Intradermal Mecholyl or Urecholine	Gauze	38	Not done	—	2.0–50.0	21.3	18	Not done	—	90.0–160.0	128.0
Back[41]	Thermal	Filter paper Plastic bag Blankets	20	4.0–52.0	27.0 ± 12.0	9.0–40.0	23.0 ± 10.0	12	72.0–157.0	125.0 ± 24.0	68.0–148.0	127.0 ± 23.0
Back[44]	Room temperature	Gauze Plastic sheet	40	6.6–37.6	21.2	6.0–38.4	21.8	20	36.4–189.4	104.0	49.6–196.1	111.5
Abdomen[43]	Thermal	Gauze Plastic sheet	45	11.5–31.5	21.5 ± 10.0		19.6 ± 8.5	23	94.0–148.0	121.0 ± 27.0		118.0 ± 23.0
Back[3]	Thermal	Plastic sheet Blanket Heat	31	1.1–101.5	37.0	8.0–93.0	36.0	10	110.6–215.4	166.0	116.0–220.0	172.0
Body[3]	Thermal	Plastic sheet Heat cradle Heat	50	1.0–88.2	25.8	6.1–111.8	36.9	21	102.0–215.0	162.8	103.0–216.9	162.4
Back[22]			8		14.2		12.7	8		89.0		87.0
			351	1.0–120.0	28.1	2.0–111.8	24.8	228	36.4–215.4	117.9	49.6–220.0	120.9

TABLE 33. *Salivary Electrolytes and Secretory Rate in Normal Children and Patients with Cystic Fibrosis of the Pancreas*

CONTROLS					PATIENTS WITH CYSTIC FIBROSIS					PAROTID SECRETORY RATE ml./5 MINUTES			
	Na mEq./L.		Cl mEq./L.			Na mEq./L.		Cl mEq./L.		Control		Cystic Fibrosis	
No. of Cases	Range	Mean	Range	Mean	No. of Cases	Range	Mean	Range	Mean	No. of Cases		No. of Cases	
14[4]	0.7–10.2	2.2	0.2–5.74	2.5	12	2.5–19.0	6.7	0.61–6.9	3.3	118	0.095	70	0.169
135[32]	Not done	—	5.1–20.1	—	20	Not done	—	15.1–65.1	—	—	—	—	—
15[13]	5.4–26.6	16.0 ±10.6	11.1–20.9	16.0 ±4.9	16	16.3–37.7	27.0 ±10.7	17.9–30.1	24.0 ±6.1	23	0.125 ±0.1	16	0.3 ±0.194
63[24]	1.8–64.8	14.7	8.9–54.0	22.1	31	6.1–60.8	26.4	12.3–54.0	29.3	63	2.75	31	3.95
13[35]	0.0–20.0	8.0	—	—	11	20.0–45.0	34.0	—	—	—	—	—	—
240	0.0–64.8	10.2	0.2–54.0	13.5	90	2.5–60.8	23.5	0.61–65.1	18.8	204	0.99	117	1.473

with cystic fibrosis the mean value for sodium was 120.5 mEq. per liter, with a range of 36.4 to 215.4 mEq. The mean concentration for chloride was 24.8 mEq. per liter, with a range of 2 to 111.8 mEq., in the control groups, and 121 mEq. per liter, with a range of 49.6 to 220 mEq., in the cystic fibrosis group. Although there were instances of some overlap in values of sodium and chloride in the control and cystic fibrosis groups, there was still striking separation of the two groups in spite of differences in methods of sweat collection, conditions for stimulation of sweat, and age of subjects.

The concentrations of potassium in sweat showed some elevation in the children with cystic fibrosis; however, considerable overlap of potassium concentrations between the normal and cystic groups made potassium concentration of no diagnostic significance. In contrast to the higher salivary glandular secretory rate described below, no definite change in rate of sweat excretion has thus far been observed.

Table 33 shows the ranges and means of the studies on saliva in patients with cystic fibrosis as reported recently.[6] These data show that the mean parotid secretory rate under various levels of glandular stimulation was 0.99 ml. per 5 minutes in 204 control cases and 1.473 ml. in 117 cases of cystic fibrosis. The mean sodium levels were 10.2 mEq. per liter in 105 control cases and 23.5 mEq. in 70 cases of cystic fibrosis. The mean salivary chloride levels were 13.5 mEq. per liter in 92 control cases and 18.8 mEq. in 59 cases of cystic fibrosis. There was a close correlation between rate of secretion and electrolyte concentration. Potassium concentrations showed no correlation with salivary secretory rate and were not different in the cystic group. There was a definite trend to higher concentration of sodium and chloride in the patients with cystic fibrosis; however, the ranges of the groups overlapped to such a considerable extent that the use of saliva in a diagnostic test for cystic fibrosis has no real value.

TEARS

Di Sant'Agnese has recently reported a statistically significant elevation of sodium and chloride in the secretions of tears; however, variation and overlap of values was considerable.[13] The mean sodium in tears of 32 control cases was 142 mEq. per liter, and 154 mEq. in 24 cystic fibrosis patients. The mean chloride was 135 mEq. per liter in the control group and 151 mEq. in the cystic fibrosis group. There was no difference in the potassium of both groups.

TRACHEOBRONCHIAL SECRETIONS

No published data are available on the electrolyte levels in the pulmonary secretions of patients with cystic fibrosis. Table 34 summarizes unpublished data from our

TABLE 34. *Electrolyte Levels in Bronchial Secretion of Patients with Cystic Fibrosis and Chronic Bronchiectasis*

	NO. OF CASES	% SODIUM/SOLIDS	% POTASSIUM/SOLIDS
Cystic fibrosis	10	1.0	0.44
Chronic bronchiectasis	10	5.2	1.15

laboratory comparing the electrolyte levels of the bronchial mucus of patients with cystic fibrosis with those of adults with chronic bronchiectasis. These data indicate that there is less sodium in the bronchial mucus of patients with cystic fibrosis than in that of patients with chronic bronchiectasis. No significant difference in potassium was found. The differences in the quantity of sodium available in both secretions suggest that the sodium may be involved in the differences in gross viscosity of the secretions in these two diseases.

THE USE OF THE ELECTROLYTE ABNORMALITY FOR DIAGNOSIS OF CYSTIC FIBROSIS

The data on concentration of sodium and chloride in sweat of children with cystic fibrosis of the pancreas indicate that the finding of a sweat sodium or chloride above 70 to 80 mEq. per liter is strong confirmatory evidence of cystic fibrosis in the presence of a clinical picture compatible with such a diagnosis. In the majority of cases cystic fibrosis is clinically suggested by a clear history and physical examination showing involvement of the respiratory system manifested as recurrent respiratory disease and the signs of pancreatic achylia manifested as more frequent, foul-smelling, bulky bowel movements. Although duodenal intubation with demonstration of depression of pancreatic enzymes was the previous tool for diagnosis, it is now apparent that the "sweat test" is the most reliable test available without the difficulties and inconveniences of duodenal intubation in children. In recent years a number of observers have reported cases diagnosed as cystic fibrosis which show little or no pancreatic enzyme depression, particularly in the earlier stages of the disease.[14, 17, 41] Many of these cases showed progression in pancreatic involvement to the low enzyme levels characteristic of cystic fibrosis of the pancreas at a later period. It is in this group with the principal picture of recurrent or chronic respiratory involvement that the "sweat test" has been of particular help in diagnosis, for previously they remained undiagnosed, requiring the passage of time for the development of clinical and laboratory evidence of pancreatic achylia.

Recent experience with the "sweat test" in children having various allergic conditions has led to some confusion in diagnosis with cystic fibrosis, since these children may have higher concentrations of sodium and chloride in the sweat than normal children. Hsia[20] recently found mean sodium levels of 42.8 mEq. per liter in allergic patients, while the mean sodium levels were 21.7 mEq. in control subjects and 103.2 mEq. in children with cystic fibrosis of the pancreas. With the plate method of Shwachman, 42 of 80 allergic patients had 3 or 4+ reactions corresponding to a sweat chloride concentration of over 75 mEq. per liter, while only 11 per cent of nearly 1000 normal children showed this reaction. Weeks and Brown[46] reported studies on 6 children with chronic pulmonary disease showing a mean concentration of sodium of 58.2 mEq. per liter and chloride of 31.5 mEq., compared to a mean of 21.2 mEq. for sodium and 21.8 mEq. for chloride in 40 control subjects. On the other hand, Anderson[2] has reported levels of sodium and chloride in the sweat of 15 bronchiectatic patients which were similar to the control concentrations. Studies of sweat in this laboratory in 14 adult patients with chronic bronchiectasis show mean concentrations of 44.8 mEq. per liter for sodium and 34.6 mEq. for chlorides,

which are slightly higher than the levels found in normal children. These levels are similar to the results obtained in normal adult controls, who show a wider range in sweat electrolyte concentration and may have higher levels. The elevated sweat electrolyte concentrations in chronic pulmonary disease and allergic conditions require further study and confirmation.

Recently there have been a number of references in the literature to cases which had a characteristic clinical picture of cystic fibrosis with levels of sweat electrolytes below 70 mEq. per liter. In a study of 44 children Anderson[2] describes 3 such cases which were diagnosed as cystic fibrosis with pancreatic enzyme depression by duodenal intubation. Shwachman wrote to Anderson that 2 per cent of 300 patients with cystic fibrosis had normal sweat electrolytes; while di Sant'Agnese indicated he had encountered an incidence of 1 per cent in 140 cases.

Such cases would suggest that the use of duodenal intubation should continue, particularly when the clinical picture is characteristic and the sweat electrolytes are not elevated. It does indicate that cystic fibrosis is a focalized disease involving the lungs, pancreas, sweat glands and other exocrine glandular systems to different degrees in each case; thus a number of cases will show a predominant involvement of one area over the others.

To illustrate the problems in diagnosis, the following cases have been selected.

CASE I. R.L. was a 9-year-old girl who had a history of chronic cough, wheezing, and shortness of breath from age 4 to 9 years. There were no bowel symptoms throughout the course of her illness. Physical examination revealed a state of malnutrition. The anteroposterior diameter of the chest was increased, and rales were heard throughout both lung fields. Chest x-ray showed emphysema and an increase in pulmonary linear markings. Duodenal fluid showed (on repeated occasions) normal pancreatic enzyme levels. The sweat had a sodium content of 165 mEq. per liter and a chloride of 178 mEq. In spite of intensive treatment with aerosol therapy and antibiotics, the chest involvement progressed in the following 3 years until death occurred from overwhelming respiratory obstruction at the age of 12 years. At autopsy there was complete occlusion of the pulmonary tree with viscid mucoid secretion and a moderate degree of exocrine pancreatic tissue involvement.

This case illustrates the usefulness of diagnosis by the sweat test in an instance in which only pulmonary disease is present without clinical and laboratory signs of pancreatic involvement.

CASE II. R.E. was a 2-year-old boy who had frequent, large, malodorous bowel movements from birth. In the 6 months prior to study a severe prolapse of the rectum had developed. Physical examination showed a moderate lag in weight and height with some protuberance of the abdomen and prolapse of the rectum. History, physical examination and chest x-ray were negative for pulmonary disease. The duodenal fluid had a depression of all pancreatic enzymes. The sweat test showed a sodium of 143 mEq. per liter and a chloride of 138 mEq. In a 2-year follow-up period there has been consistent pancreatic involvement without any signs of respiratory disease except for occasional mild colds.

This case is an example of a child with cystic fibrosis in whom little or no respiratory disease is present. Once more the sweat test is of great significance as an aid to diagnosis.

CASE III. A.P. was a 5½-year-old boy with a history of recurrent vomiting, high fever, severe dehydration and convulsions during the early summer months of the previous 3 years. At the time of hospitalization at the Children's Hospital of Philadelphia he had been vomiting for 1 day following the onset of a heat wave in June. His temperature was 98° F. There was no history or physical evidence of pulmonary or intestinal disease. Serum chlorides on admission were found to be 88 mEq. per liter, and serum sodium was 136 mEq. A sweat test showed a chloride of 230 mEq. per liter and a sodium of 207 mEq. Treatment with parenteral salt-containing solutions produced complete improvement. In the subsequent follow-up period there has been no recurrence of the annual disturbance and a disappearance of lassitude during the heat of the summer season with supplementary intake of salt. The boy shows good growth and has no evidence of respiratory or intestinal disease at this time. The duodenal fluid has normal enzyme activity, and repeated sweat tests have showed a marked elevation of the sweat sodium and chloride. No other disease of the central nervous system or adrenal glands has been found by clinical or laboratory study. No sibling history is available for cystic fibrosis, since this is the only child in the family.

This case raises a question as to whether such an abnormality indicates that this boy has a type of cystic fibrosis in which the sweat glands are the only site of involvement. This patient will be reported more completely in the near future.

FACTORS CONTROLLING THE SECRETION OF SWEAT

Since both the methods of sweat collection and the physiologic disturbance resulting from the abnormality in sweat of patients with cystic fibrosis depend on various factors involved in sweat secretion, it is pertinent at this point to review these factors briefly. Reviews of the physiology of sweating have been made by Kuno,[27] Robinson[37] and Schwartz.[42]

Neurogenic secretion of sweat is produced by direct or reflex stimulation of centers in the spinal cord, medulla, hypothalamus or cerebral cortex. Non-neurogenic sweating, i.e., direct activation of the sweat glands, may result from the action of local heat and cholinergic and other chemical agents. The rate of sweating rises with environmental temperature and with increasing metabolic rate during exercise. Maximal sweat rates have been reported to reach 2 to 3 liters per hour in adult males under conditions of intense stimulation.[37] In warm climates there is considerable acclimatization to heat, the process of adaptation of the body consisting in a cardiovascular adjustment and a change in sweat electrolyte concentration following prolonged exposure to heat. In normal adults there is wide variation in sweating rate even under identical conditions of stimulation. In the same person there are considerable regional differences in the rate of sweating and in the con-

centration of the electrolytes of sweat. The palms, soles, head, neck and trunk sweat much more than the extremities. Some difference has also been reported between children and adults; i.e., Kuno[27] states that the secretory rate of sweat below two years of age is twofold that of the adult.[27] Humidity has been observed to increase the maximal secretory rate of sweat by suppressing evaporation; however, other studies have not confirmed this finding. Similarly, there are conflicting reports on the relationship between salt intake and secretory rate. Some investigators report the secretory rate to be increased by negative salt balance and decreased by positive salt balance.[42] If true, this mechanism could be of some importance in the patients with cystic fibrosis who have such a great increase in the salt loss by the extrarenal route of sweating. In addition, water balance may be important, since dehydration may reduce sweating rate when superimposed on salt depletion.[42]

TABLE 35. *Comparison of Electrolyte Concentration of Sweat in Normal Children and Adults*

SUBJECT	NO.	SODIUM (mEq./L.) Range	SODIUM (mEq./L.) Average	CHLORIDE (mEq./L.) Range	CHLORIDE (mEq./L.) Average
Children	30	9–39	26	11–66	37
Adults	20	27–87	56	19–82	52

The electrolyte concentration of sweat varies directly with all the factors described above for secretory rate. However, once more, as in secretory rate, there are wide variations among subjects in various areas of the body, at different ages and under certain environmental and dietary conditions. Table 35 shows the values of the sodium and chloride of sweat obtained by Anderson[2] with Mecholyl stimulation on a small group of normal children and adults. The adults had a wider range and a higher mean sodium and chloride concentration than the children under similar conditions of stimulation. The importance of this potential difference between adults and children becomes clear in the studies of parents and relatives of patients with cystic fibrosis, in whom higher levels have been occasionally reported.[12, 43] It accentuates the difficulty of evaluating the results of such screening tests as Shwachman's plate test when used in older persons.

In the normal person sweat is usually a hypotonic fluid leading at times of intense sweating to dehydration more rapidly than to salt depletion. In the patient with cystic fibrosis, however, sweat approaches more closely the tonicity of the extracellular fluid; consequently its loss in periods of more intense sweating can lead to signs of salt depletion as well as of dehydration. This phenomenon will be discussed subsequently in the section on the pathophysiologic disturbance of electrolytes in cystic fibrosis.

The concentration of sodium chloride in thermal sweat of adults has been reported to range between 18 and 97 mEq. per liter by 86 different investigators summarized by Robinson.[36] Concentrations of sodium chloride above 80 mEq. per liter are found in samples from local skin areas enclosed under impermeable barriers such as plastic or other materials.[42] Normal persons who become acclimated to areas of intense heat have reduced salt concentrations in the sweat. The level of salt concentration increases and falls with a rise and fall in dietary intake respectively.

The sweat glands under continued thermal stimulus decrease in their adaptive capacity to produce sweat of a low salt concentration. This phenomenon is regarded as evidence of peripheral glandular fatigue.[42] The sweat excreted by "fatigued" sweat glands resembles the sweat excreted by patients with cystic fibrosis. Speculations as to what relationship might exist here invite further investigation of this problem.

METHODS OF SWEAT COLLECTION

The methods of collecting sweat are influenced by the same physiologic factors discussed above, whether one uses thermal or cholinergic stimulation. Fortunately, the usual differences between the normal and cystic levels of electrolyte in sweat are sufficiently great to make a careful control of temperature, humidity and site of no great significance for diagnosis. It is more important that each clinic interested in performing the "sweat test" develop its own experience with a technique in which normal limits can be defined.

A word of caution has to be given about any of the sweat-collecting methods involving heat as a stimulus. Recently sudden death from heat prostration during a sweat collection test has been reported.[31, 34] Avoidance of prolonged heating and adequate hydration before and during a test would tend to minimize the potential for such disasters.

Three methods commonly used for sweat collection in children are outlined below. Since the initial report of Darling and di Sant'Agnese, a large number of modifications of their methods have appeared.

1. The method of Darling and di Sant'Agnese as modified by Shwachman[39] has been widely used. In this method, sweat is obtained in a local area by a thermal stimulus.

No special preparation of the patient is necessary. The back is washed with sterile water and dried. A 3-inch square gauze pad, previously weighed in a flask, is placed on the back. A slightly larger piece of plastic sheeting is placed over this and taped to the skin with adhesive. The patient is then placed in a plastic bag which has a tight collar and a zipper in front. He is covered with a blanket. At the end of 30 to 90 minutes, depending on the rate of sweating, he is taken from the bag. The plastic sheeting is removed. The sweat-soaked gauze pad is returned to the previously weighed Erlenmeyer flask with forceps. The weight is determined once more, and the difference between the 2 weights represents the amount of sweat collected.

Then 50 ml. of distilled water are added to the flask and the chlorides determined by the method of Schales.[38] One milliliter of the solution is sufficient for this determination. Five milliliters of the solution are diluted to 50 milliliters and the sodium concentration determined with the flame photometer.

2. The method of Barbero, Kim and McGavran[3] involves obtaining sweat from large body surfaces by a thermal stimulus.

The subject is bathed with soap and water, washed off thoroughly with water and dried. He is then placed nude on a plastic sheet and subjected to a moderate thermal stimulus for 20 to 40 minutes. Sweat is collected with a tuberculin syringe from the surface of the plastic sheet and the back of the patient. In the infant under 6 months the thermal stimulus is conveniently obtained through the use of a Chapple Isolette set at 95° F. and 100 per cent humidity. A diaper is placed on the infants and covered with plastic pants or plastic sheeting to cut down contamination from urine. In older infants and children a heat cradle with a 100 watt bulb fastened to the top is placed over the trunk of the subject with several blankets over the entire apparatus tucked in tightly about the neck and legs to prevent evaporation. By this method 2 to 20 ml. of sweat are obtained.

The sweat is then centrifuged for 3 minutes to clear it of epithelial and undissolved debris. A 1:100 to 1:200 dilution is then made and analyzed for sodium on a flame photometer. The chloride level is determined by the method of Schales[38] without previous deproteinization. A total of 0.3 to 0.4 ml. of sweat will suffice for these 2 determinations.

3. The method developed by Anderson[2] and Mauer and West[33] involves sweat collection in a local area of the forearm after injection of a cholinergic drug.

Sweat is collected from the ventral surface of the forearm after the intradermal injection of 2 mg. of methacholine hydrochloride.* After the injection the site and surrounding area are well washed with ether and distilled water and dried thoroughly. The injection site is checked for leakage. The area is then covered with a gauze pad measuring 3 inches by 3 inches (Johnson and Johnson), and with a square of plastic taped to the arm by adhesive plaster.

Before use, the pads are well washed in distilled water to remove traces of electrolytes and are dried in the oven. They are weighed on an analytical balance in glass-stoppered 50-ml. flasks before and after sweat collection. The gauze is carefully handled with forceps, and the flasks are not touched by unprotected hands. Quantities of sweat over 100 mg. are suitable for estimation. Usually about 100 to 300 mg. of sweat are obtained after the gauze has been left on the arm for 1 hour. At the end of the collection period the pad is removed with forceps and returned to the flask. Twenty milliliters of distilled water are added to the flask, which is then shaken at intervals for 1 hour. Sodium and potassium concentrations are determined on a flame photometer. Chloride is measured by the method of Schales.

SCREENING TESTS FOR SWEAT CHLORIDE

At present two screening methods have been developed to test for elevated levels of chloride in the sweat. These tests should not be utilized to make a definitive diagnosis, since all screening tests tend to have a low incidence of false negatives and a large number of false positives. Although these tests may be useful as screening tests, the authors'

* Mecholyl—Merck, Sharp & Dohme.

experience with them suggests that they also may create considerable confusion, especially when not carried out with the scrupulous precautions prescribed by Shwachman.[45] Carefully carried out, these tests may be of value when supervision and help for interpretation are available from a physician with wide experience with these tests. As simple screening tests, occasionally used by clinics or private physicians, they have much less reliability.

Table 36 demonstrates that 18 subjects with sweat chloride levels below 75 mEq. per liter gave 3 to 4+ reactions, while sixteen had 3 to 4+ reactions with sweat levels greater than 75 mEq. per liter. Such lack of correlation between the plate screening method and a sweat collection technique of established repute considerably limits the usefulness of the agar plate method.

TABLE 36. *Correlation between Shwachman Plate Test and Sweat Chloride*

	SWEAT Na (mEq./L.)				
	0–25	26–50	51–75	76–100	Over 100
1+	9	5	6	0	0
2+	3	2	3	1	0
3+	1	8	6	1	1
4+	0	1	2	3	11

Unpublished data by Dr. David Hsia, Chicago.

1. The following description of the plate test is given as stated by Shwachman.[40]

A finger or foot impression is made directly on the surface of the agar plate after having washed and dried the area, allowing 20 minutes to elapse before the test. The agar plate is made up as follows:

To prepare 500 ml. of the mixture, 25 gm. of agar are dissolved in 500 ml. of boiling water. When the agar is melted, 4.2 gm. of silver nitrate are added to the agar and thoroughly stirred. Then 2.5 gm. of potassium chromate are added, and the mixture is stirred for a few minutes. The warm mixture is poured into plastic Petri dishes and permitted to harden. The chloride test medium thus prepared can be stored in a refrigerator in a sealed plastic bag for prolonged periods without deterioration. At room temperature the plates can be kept for a number of days without any significant alteration.

When little chloride is present on the skin surface, as after the hands have been washed in water and dried, the imprint is barely detectable on the surface of the plate. If considerable chloride is present on the skin surface, an intense whitish-yellow discoloration occurs immediately. The imprint is rated between 1+ and 3+. A concentration less than 60 mEq. per liter will produce little or no reaction (1+), whereas one over 250 mEq. will give an intense discoloration (3+).

2. Webb and Geiger[45] of Toronto Children's Hospital devised another screening method, based on the same chemical reaction. Whatman no. 2 filter paper is impregnated with 2 per cent silver nitrate, and the patient presses this moistened paper between the thumb and index finger for 1 minute. A 10 per cent solution of potassium dichromate is added to the filter paper, and the area of the fingerprint remains yellow if the test is positive.

EFFECTS OF SALT DEPLETION IN CYSTIC FIBROSIS

The influence of sweating on water and salt metabolism in normal persons under normal conditions of temperature can be considered negligible for practical purposes. The mineral reserves of the body are such that sweating of moderate intensity can be easily handled. The extrarenal sodium chloride loss of patients with cystic fibrosis, however, plays an important role in their well-being. A brief review of the effects of heat on the body may help to clarify some of the problems of heat prostration in the child with cystic fibrosis.

There are many well documented experimental studies on the reaction of the healthy human body to hot climates.[1, 10] On the other hand, exact data are lacking on the extra requirements to compensate for the salt loss in sweat of children with cystic fibrosis.

The different syndromes that can result from lack of water and sodium chloride* are well known. Frequently a further distinction between these two is clinically rather difficult. In experimental work in dogs Elkinton and Danowski[15] demonstrated that the loss of sodium chloride is more deleterious than the loss of water. As an example of pure sodium chloride deficiency it is worth recalling an old clinical observation. The agonizing cramps of patients with choleraic diarrhea who drink water freely can be completely alleviated by adding sodium chloride to their liquids. One of the results of withholding solid feeds as treatment for diarrhea is severe sodium deficiency in these patients.

As to the extra salt requirements of coal miners in Wales under conditions of hard work and high temperatures, Hancock[19] mentions that "by such expedients as eating red herrings or highly salted bacon, coal miners guided by appetite alone, usually prevent the occurrence of symptoms."

The literature on free-choice feeding indicates that animals and man have specific appetites which guide them to selections appropriate to their needs.[28] In this connection it is worth mentioning that clinicians have long observed the craving for salt in children with cystic fibrosis. One wonders, though, whether this kind of teleologic mechanism can really be supposed to be present. Yudkin[48] observed that salt-deprived adrenalectomized animals freely chose a sugar solution in preference to a salt solution, and consequently died sooner.

In a personal account of the effects of sodium chloride depletion with free drinking of water McCance[30] described subjective anorexia and nausea and "cramps all round the chest produced by coughing, great fatigue and finger cramps." Objective findings were changes in facial contours, delayed diuretic response and negative nitrogen balance. He

* For salt loss in diabetes, salt-losing nephritis, cerebral conditions, and so on, see other papers of this volume.

mentions, too, the development of "an extraordinarily interesting state in which they were content to sit and do nothing in a chair, sometimes for hours on end."

The physician caring for children with cystic fibrosis will recognize here some of the symptoms of his patients.

In severe heat, as in central India, extreme losses of water and salt are possible. A weight loss of 15 kg. in an adult man was recorded by Hunt.[21] Sweat losses of 1500 to 2000 ml. (3.5 to 5.0 gm. of sodium chloride) in 2 to 4 hours can easily be produced experimentally by severe muscular exercise in a temperature of ±95° F. Kuno[27] concludes "that the maximum amount of sweat per hour in the summer may be between 1½ and 2 kg. Strenuous muscular activity increases internal heat production 10-15 times, and the resulting copious sweating can easily lead to severe H_2O and NaCl depletion." Kuno approximated secretory

TABLE 37. *Approximate Quantities Secreted by Excretory Glandular Systems*

SECRETION	TOTAL WEIGHT OF GLAND	AMOUNT OF SECRETION PER DAY	AVERAGE AMOUNT OF SECRETION/10 GM. OF GLAND
Saliva	70	1.5	214.0
Pancreatic juice	80	1.0	125.0
Bile	2000	1.5	7.5
Breast milk	200	3.0	150.0
Sweat	40	10.0	2500.0

quantities produced by different glandular systems, as shown in Table 37. Here the high level of secretion of the sweat glands is clearly evident.

The response of the cardiovascular system to heat has been thoroughly studied.[8] Initially the minute volume of blood circulating through the skin increases greatly, promoting heat elimination. The acute diversion of blood to the periphery produces early signs of peripheral collapse, such as rapid pulse, diminished stroke volume, severe postural hypotension and peripheral vascular engorgement. Cardiovascular adaptation to heat occurs to a great extent during the first four days of exposure to work in heat.

In Table 38 the three clinical states resulting from the influence of heat on the adult human body are summarized. Frequently the clinical picture is a combination of these syndromes.

Although there is a multitude of studies on heat effects in adults, the pediatric literature offers hardly any description of the reaction of children. Cardullo[7] studied the effect of a heat wave in New York on healthy and sick children, and raised many important questions on the problem of heat prostration. His findings were as follows: (*a*) Severe affliction by heat seemed associated with absence of sweating; (*b*) pa-

tients with pre-existing central nervous system disease showed a more serious reaction which was sometimes fatal; (*c*) the majority of infants under two years of age reacted to heat with a rise in body temperature. A factor of great importance in the reaction of the human body to heat is the development of fatigue of the sweat glands. When stimulation is prolonged, the sweat glands are less capable of producing sweat of low electrolyte concentration after a period of secretion. The volume

TABLE 38. *Effects of Heat in Man*

	HEAT CRAMPS	HEAT PROSTRATION	HEAT STROKE
Mechanisms	Sodium depletion	Circulatory failure	Failure of heat regulation
Signs	Muscle cramps	Lassitude, syncope	Sudden coma and convulsions
Rectal temperature	Normal	Normal or slightly elevated	>39° C.
Skin temperature	Normal	Normal or cold	Hot
Sweating	Present	Present	Absent
Skin, appearance	Normal	Pale	Red, dry, occasionally maculopapular rash
Blood pressure	Normal	Decreased	Elevated except in extremis
Serum sodium	Decreased	Decreased or normal	Normal
Serum CO_2, pH	Normal	Normal	Decreased, lactic acid increased
Urine	Sodium chloride decreased	Normal	Albumin present
Preceding and promoting factors	Excessive sweating, hard work and free drinking of H_2O	Prolonged standing	Alcoholic intake
Prognosis	Good	Good	Grave
Onset	Gradual	Sudden	36–72 hours after onset of heat wave

of sweat produced gradually diminishes, and less water is available for evaporation. The result is increased electrolyte loss and decreased heat loss. Once temperature elevation sets in, a vicious cycle develops, as the human body as a whole reacts to rise in temperature according to Van't Hoff's law: i.e., with each degree C. the metabolic turnover rate increases 13 per cent. This explains the extremely high temperatures recorded in some of the heat casualties.

Kessler et al. [26] were the first to call attention to the frequent occurrence of heat prostration in cystic fibrosis. In light of the extensive pulmonary involvement in children with cystic fibrosis, it is of interest to find that Park had earlier observed pneumonia in the upper lobes to

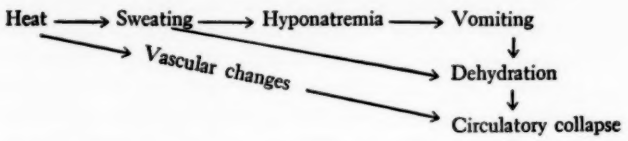
be one of the commonest predisposing factors in the development of hyperpyrexia in hot weather.[7] In Kessler's patients vomiting was a major initial symptom, with the subsequent onset of lethargy and the development of dehydration and signs of circulatory collapse. The occurrence of vomiting in Kessler's patients seemed to play an important role in their dehydration and electrolyte loss. There was no real hyperpyrexia with sweat gland failure. In pediatric patients with the adrenogenital syndrome one of the presenting symptoms of sodium deficiency is frequently unexplained vomiting. Apparently vomiting is more liable to result from hyponatremia in the younger patient and is less frequent in adults.

Data from the literature make it clear that with normal sweat electrolyte content salt losses of 20 gm. daily may result from high sweating rates in unacclimatized men.[36] The estimated total body sodium chloride of adult men is 175 gm. The estimated daily sodium chloride intake is variable, but somewhere in the order of 10 gm. for the North American adult diet. Given the four to seven times normal sodium chloride concentrations in sweat of children with cystic fibrosis, it is readily understood that salt deficiencies can occur easily and rapidly. Recent determinations in our laboratory have suggested that the sweat glands of children with cystic fibrosis have some capacity for acclimatization to hot weather. It is common experience that children with cystic fibrosis suffer heat prostration only in the earlier part of the summer. After acclimatization of his sweat glands the patient with cystic fibrosis may be better able to economize his salt stores.

Although there may be potential undesirable effects of high salt intake in adults, the foregoing considerations have led us to consider the supplementary addition of salt to the diet to be of great importance in the prevention of heat prostration in patients with cystic fibrosis. With the addition of 3 to 6 gm. of salt daily during the warm months of the past several years we have not encountered any cases of heat distress in the patients of this Clinic. Many parents commented that the prior lassitude and crankiness in their children diminished with this minimal supplementation of salt. There is a serious need for study of salt requirements under conditions of increased heat in the patient with cystic fibrosis.

TREATMENT OF ACUTE HEAT PROSTRATION

As stated above, the problems of heat prostration in children with cystic fibrosis result from salt depletion and dehydration, which lead to circulatory collapse. For therapeutic purposes the mechanism of heat prostration in patients with cystic fibrosis can be schematically summarized as follows:



The basic principles of treatment of hyponatremia and dehydration have been extensively outlined in other papers in this volume. In essence, the treatment of the patient with cystic fibrosis is similar to the treatment of any other patient with hyponatremia and dehydration; however, the cystic child with heat prostration may have a more acute course and greater state of salt depletion, which may require the use of 1 to 2 per cent saline solution for correction. Lowe and di Sant'Agnese[29] have recommended 10 ml. of normal saline per kilogram intravenously in 15 minutes, with a total equal to 10 per cent of the body weight given as normal saline in the first 24 hours. In our experience salt solutions of greater concentrations may be needed.

Special pitfalls in the treatment of these patients may be the development of water intoxication by infusion of fluids relatively too low in salt concentration and the possible presence of potassium deficiency with elevated levels of serum potassium (a peculiar kind of starvation in the midst of plenty). This last occurrence will of course require the use of potassium-containing solutions as a subsequent therapeutic step, once urination has occurred.

RESPIRATORY ACIDOSIS

Respiratory acidosis occurs in patients with cystic fibrosis of the pancreas in an advanced state of respiratory involvement. The sequence of events occurring during chronic pulmonary disease is briefly summarized here. The ability of the lungs to rid the body of carbon dioxide is curtailed by the increased resistance to airflow in the tracheobronchial tree caused by the abnormally viscid mucus, obstructing the entire bronchial passage. West et al.[47] in a study of the pulmonary function of six children with cystic fibrosis found that the alveolar function is severely impaired, indicated by abnormal distribution of tidal air in the alveoli. There is increased dead-spacelike ventilation and a reduction in the total lung capacity. The ventilatory function is impaired as the altered chest configuration secondary to emphysema results in a position of poor mechanical advantage for the muscles of respiration. The chronic infectious process may lead to permanent damage of the pulmonary tissue, and the elasticity of the lung is decreased. The biochemical consequences of these disturbances in pulmonary function are increased carbon dioxide retention and arterial anoxia, initially with exertion and later at rest.

The bicarbonate-carbonic acid ratio decreases (<20:1); consequently there is increased H ion concentration, manifested as decreased blood pH. Bruch[6, 23] found a reduced blood oxygen tension in all the patients with cystic fibrosis who were studied. Since two of these patients had little evidence of pulmonary disease, she postulated that some other mechanism than hypoventilation might be present.

The medullary respiratory center becomes increasingly less sensitive to changes in carbon dioxide at the high levels of carbonic acid concentration in the blood, and anoxia replaces carbon dioxide changes as the stimulating factor for the respiratory center.

All these changes develop over a prolonged period of time, and the temporarily established biochemical equilibria offer a greatly diminished reserve in situations of respiratory stress.

In the treatment of chronic respiratory acidosis the most important consideration should be the treatment of the underlying pulmonary disorder. The combined used of antibiotics and mechanical clearing of the tracheobronchial tree in a preventive program will tend to defer too extensive derangement. In situations of acute exacerbations additional digitalization and occasional use of mechanical respirator devices have proved to be of great value.

Although studies of emphysema in adults and those in children with cystic fibrosis have shown that respiratory acidosis can be aggravated by oxygen therapy, our clinical experience with oxygen has not shown adverse effects of oxygen administration to the patient with cystic fibrosis. Most of the children in acute respiratory distress experience considerable relief with oxygen administration and wish to have its use. We have not observed depression of respiration by this administration. With older patients the possible danger of carbon dioxide narcosis, occasionally seen in connection with oxygen therapy, must be kept in mind.

SUMMARY

1. A review of the elevated concentrations of electrolytes in the different secretions of the patient with cystic fibrosis, as reported by many different workers, demonstrates that an elevation of sweat sodium and sweat chloride above 80 mEq. per liter has been considered definite laboratory evidence of cystic fibrosis of the pancreas in the presence of a clinical history of either respiratory or gastrointestinal symptoms, or both, characteristic of the disease, or laboratory evidence of such.

2. Heat prostration is an acute complication in the patient with cystic fibrosis. The high sodium chloride secretion and the extensive sweating during acute changes in heat result in vomiting, lassitude, de-

hydration, hyponatremia and circulatory collapse in children with cystic fibrosis.

3. Supplementary salt intake of 3 to 6 gm. of salt per day is of great importance in the prevention of heat prostration and lassitude during the warm seasons of the year for the patient with cystic fibrosis.

4. Therapeutically, heat prostration is an acute emergency requiring a 1 to 2 per cent sodium chloride solution as initial parenteral fluid therapy for the hyponatremia and dehydration.

5. Respiratory acidosis resulting from the poor air exchange in the lung of the child with cystic fibrosis is a serious manifestation of this disease. The use of antibiotics to suppress infection and mechanical clearing of the tracheobronchial tree are our main means of treatment at this time.

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1740 Bainbridge Street
Philadelphia 46, Pennsylvania

FLUID THERAPY IN CONGESTIVE CIRCULATORY FAILURE

MARY ALLEN ENGLE, M.D.

Fluid and electrolyte disturbances in congestive circulatory failure result primarily from inefficiency of the heart as a pump, whatever the cause, and secondarily from excessive renal retention of sodium and water. Therapy for the condition is directed toward improving the efficiency of the heart by the use of a digitalis preparation and rest, and toward restoration of a better fluid balance by accessory measures that speed elimination of accumulated fluid. Then the underlying cause of the cardiac difficulty is treated by whatever medical or surgical means are appropriate.

MECHANISMS OF CONGESTIVE FAILURE

The precise mechanisms involved in the development of congestive cardiac failure are not yet fully understood, but the following sequence of events seems a reasonable scheme in the light of current information. The difficulty begins when the heart is no longer able to fulfill its work load, either because of an obstruction against which it must pump, or because of an excessive return of blood into the heart, or damage to the myocardium—these and other causes, singly and in combination.

When the output of the heart fails, in relation to the demands placed on it, incomplete emptying occurs in the most distal chamber that is overburdened. For example, in aortic stenosis or a large patent ductus arteriosus with pulmonary overcirculation, or in mitral insufficiency or in myocarditis, this chamber is the left ventricle. In mitral stenosis the left atrium is the first chamber to fail to empty completely, and in severe pulmonic stenosis or idiopathic pulmonary hypertension the right

From the Department of Pediatrics, New York Hospital-Cornell Medical Center, New York City.

ventricle is the first to be affected. With incomplete emptying the pressure becomes elevated at the end of the filling phase of that chamber (the end diastolic pressure of the ventricle, for example). This elevation of pressure puts a greater load on the next most proximal chamber or venous system, which in time becomes unable to empty itself completely, with a resultant pressure elevation. In backward fashion this chain of events includes each successive chamber or venous system in turn until there is elevation of systemic venous and capillary pressures. If there has been hypertrophy of the myocardium or some dilatation of the chamber because of the pre-existing load, increased dilatation of the chambers is added as the residual volume and elevated pressure in each are increased.

About the time that early elevation of venous and capillary pressures appears, a separate series of events involving the adrenal glands and kidneys sets into action a mechanism that alters fluid balance by retention of sodium and of water. The exact manner in which these reflex changes are initiated or brought about has yet to be demonstrated. Perhaps there is a receptor sensitive to slight changes in blood volume or pressure or flow that through a hypothalamic center stimulates increased production of aldosterone-stimulating hormone. The next step is known: In the adrenal cortex are produced large amounts of aldosterone, whose effect is to increase renal tubular reabsorption of sodium. Reabsorptive capacity for water is unimpaired; so water retention accompanies sodium retention, and the signs we recognize as congestive cardiac failure appear: expanded extracellular volume, further elevation of venous and capillary pressures, and the presence of congestion in the systemic and/or pulmonary circuits with rapid weight gain and edema. As the circulatory system becomes progressively less competent and the effective cardiac output further reduced, there ensue additional renal changes attributable to decreased glomerular filtration rate.

MANIFESTATIONS OF CONGESTIVE FAILURE

In the pediatric age group most instances of congestive cardiac failure are encountered during infancy and only about 10 to 15 per cent throughout the rest of childhood. In similar proportions, most of the signs of cardiac failure are those of right-sided decompensation, even though the left side of the heart is at fault in the series of events leading to the cardiac failure. It is rare to detect rales in the lung fields of an infant in failure, for example, unless the lesion is one which leads to left ventricular failure or obstruction of pulmonary venous outflow at the same time that the pulmonary capillary bed is bombarded from the pulmonary arterial side by increased pulmonary blood flow through a large left-to-right shunt. Large ventricular septal defects and coarctation

of the aorta associated with a patent ductus are two such lesions. Even in older children in failure, pulmonary edema is uncommon. It is found chiefly in children with severe, chronic renal disease with hypertension. Then attacks of acute pulmonary edema or paroxysmal nocturnal dyspnea as well as more persistent signs of pulmonary venous congestion occur.

The signs of congestive cardiac failure in the pediatric years, then, are evidences of cardiac embarrassment plus signs of systemic venous engorgement and, rarely, pulmonary venous congestion. The heart is enlarged and beating rapidly; often a gallop rhythm is heard. Under certain circumstances, such as myocarditis or pericarditis with effusion, the *heart sounds* may be muffled. In other conditions, such as some of the congenital cardiac anomalies leading to pulmonary arterial and right ventricular hypertension, the heart sounds are as loud and banging as they would be under conditions of better compensation. So, too, the *blood pressure* reflects more the underlying cardiac condition with its high, normal or low pressure than it does the status of heart failure per se. The pressure is likely to be somewhat lower, however, in the patient in cardiac failure than during compensation.

Cardiac *murmurs* are variable in the failing heart. None may be heard, as is often true with endocardial fibroelastosis, or a new one may appear, as in myocarditis, presumably from changes in the size of the valve rings in relation to the size of the cardiac chambers and vessels. In congenital cardiac anomalies, murmurs known to have been present previously may disappear or change during cardiac failure, only to reappear when compensation is restored. This is true of the diastolic component of the continuous murmur of patent ductus arteriosus, for example. It is wise to reserve interpretation of heart murmurs under these conditions until the heart is no longer failing.

Respirations are rapid and often labored, with an expiratory grunt, dilatation of the alae nasi, and retraction of the suprasternal notch and lower ribs anteriorly at the level of the diaphragm. An ominous sign is use of accessory muscles of respiration, the lower jaw pulling down and neck muscles tensing with each inspiration. With much pulmonary congestion a cough may be present. Sometimes this is the first sign that calls the mother's attention to the fact that her baby is ill.

Like other signs of predominantly left-sided cardiac failure, *orthopnea* is unusual. It may be present, though, even in the young infant. The mother may be aware of it through a trial-and-error method of trying to comfort her restless baby, when she learns that he seems more comfortable upright against her shoulder. The semi- or bolt-upright position may be spontaneously assumed by older infants and children.

Skin color may vary from normal to ashen gray or mottled (especially with peripheral circulatory failure) or cyanotic. *Cyanosis* under these

conditions may be due to peripheral venous stasis, so that more than the usual amount of oxygen is removed from capillary blood, and it more nearly resembles venous blood in oxygen saturation. Hence the patient may look cyanotic. Or there may be inadequate oxygenation of the blood perfusing congested lung fields, so that there is subnormal oxygen saturation of pulmonary venous blood and the blood in the left side of the heart and systemic circulation. Often a superimposed respiratory infection is the final insult that tips an overburdened heart into failure. This, too, may contribute to cyanosis on a respiratory basis. Finally the underlying heart condition may be a malformation with a persistent or potential venous-arterial shunt, whereby an elevation of pressure in the right side of the heart or pulmonary artery and/or a drop in pressure in the aorta or left side of the heart favors a right-to-left shunt and cyanosis. Here, as in inadequate oxygenation of blood in the lungs, the oxygen saturation is reduced below the normal 95 to 96 per cent.

Engorgement of the liver is the most sensitive index of cardiac failure in the infant and young child. Acute distention is associated with a tender as well as enlarged liver which has lost its sharp edge and descends several centimeters below the costal margin, often as far down as the level of the umbilicus and sometimes to the iliac crest. Liver engorgement of longer standing may cause no discomfort on palpation. With insufficiency of the tricuspid valve, and occasionally with tricuspid stenosis, pulsations are palpable at its margin. Pressure on the liver causes an increased fullness of the veins in the neck, though in an infant's short or chubby neck this may be difficult to see.

Visible fullness of neck veins or other peripheral veins should be sought, but is less easy to detect or evaluate in the very young than is hepatic enlargement.

A sudden increase in weight, indicative of fluid accumulation rather than normal growth, may be detected on the physician's scales, if previous weights are available for comparison, before overt *edema* is noticed. Pitting, dependent edema is a late sign of cardiac decompensation in an infant; the true nature of his difficulty is usually recognized and treated before edema is manifest. In the baby this pitting, dependent edema is likely to be widespread and involve not just the extremities, but the face as well; the face is the dependent area of the infant accustomed to sleeping on his stomach. In older, ambulatory members of the pediatric age group, as in adults, pedal edema may be the earliest observed edema. The shoes feel too tight, or ankle or instep straps leave a mark.

Other symptoms of congestive cardiac failure include fatigue on ordinary or slight exertion. The infant may become so tired or short of breath after taking only an ounce or two from his bottle that he cannot take more even though he may seem hungry. Actual loss of appetite at all ages may be noted. Failure to gain weight properly is common, espe-

cially in infancy. Unusual drowsiness or irritability may be noted. Fortunately, loss of consciousness or coma occurs only rarely and in the desperately sick.

CAUSES OF CONGESTIVE FAILURE

The more important causes of cardiac failure in the pediatric age group are listed in Table 39 in order of decreasing frequency and according to the usual age at onset as well as suddenness of appearance.

TABLE 39. *Causes of Cardiac Failure*

GRADUAL, PREDICTABLE	SUDDEN, UNEXPECTED
Infancy (0–12 Months)	
Congenital malformations, especially:	Paroxysmal supraventricular tachycardia
Complete transposition of great vessels	Endocardial fibroelastosis
Ventricular septal defect, large	Myocarditis
Coarctation of aorta with patent ductus and often with ventricular septal defect	Pericarditis with effusion
Total anomalous pulmonary venous return to right atrium or tributary	Severe respiratory infections, as bronchiolitis
Atrioventricular canal	Abrupt circulatory overloading from excessive parenteral fluids or transfusion
Patent ductus arteriosus, large	Infants born to diabetic mothers
Aortic or mitral atresia	Coronary artery disturbances:
Single ventricle	Anomalous origin of coronary artery from pulmonary artery
Anemia, severe	Coronary sclerosis
	Glycogen storage disease of myocardium
	Cardiac tumors
Childhood (1–14 years)	
Rheumatic heart disease	Acute glomerulonephritis
Hypertensive cardiovascular disease with chronic, severe renal disease	Acute rheumatic fever
Anemia, severe, chronic, and especially with associated hemochromatosis	Myocarditis
Cor pulmonale with cystic fibrosis of pancreas	Pericarditis with effusion
Hyperthyroidism	
Congenital cardiac anomalies plus severe infection	
Others, such as lupus erythematosus, neuromuscular dystrophies, etc.	

Approximately 85 to 90 per cent of the examples of congestive cardiac failure seen by the pediatrician are in babies in the first year of life, and most of these occur in the first 6 months of life. Sometimes the failure comes on suddenly and unexpectedly in a baby who has previously been thriving. More often a heart murmur or feeding difficulties or failure of the baby to gain forewarns the pediatrician that cardiac

failure may occur. Alert to this possibility, he observes the infant at more frequent intervals than he might for ordinary well-baby care, because early recognition and treatment of decompensation seem safer and easier than if the failure is far advanced. Taking into consideration the experience of the physician as well as the fact that the cardiac failure has been recognized early in its course, treatment of this baby may be on an ambulatory basis without the need of hospitalization. For babies who appear quite sick or have a sudden onset of cardiac failure, however, hospitalization is wiser, for closer observation as well as for the use of equipment not readily available in the home.

THERAPY

Treatment of congestive cardiac failure, regardless of its cause, is designed to render the cardiac action more effective by use of digitalis and rest as well as by whatever medical or surgical means are appropriate to treat the underlying cause of the failure. Furthermore, therapy is directed to restoration of a more nearly normal fluid and sodium balance by elimination of excessive amounts accumulated and by prevention of future abnormal retention of sodium and water.

Digitalis and Digitalis Preparations

Digitalis in some form is the drug of first choice for the patient in cardiac failure. Several preparations are available. The selection of one over another depends on the urgency of the situation as well as on the familiarity of the physician with a particular drug. The pediatrician will be well equipped to handle any situation of cardiac decompensation if he knows how to use a rapidly acting intravenous preparation, as lanatoside C, and at least one oral preparation, preferably a purified glycoside such as digitoxin or Digoxin.

The usual digitalizing dose of each preparation will be given below. There is some variation in response between patients at the same dosage level, but this variation seems chiefly related to the underlying condition that brought about the cardiac failure. Infants require larger doses per kilogram of body weight than do older children. In estimating the digitalizing dose for a patient, when there is a range of values from which to choose, one should aim for the lowest dosage schedule that is effective. No greater benefit will accrue from larger doses, and there is a greater chance of encountering toxicity. If the desired effect has not been achieved by this low dose, in conjunction with the other anticongestive measures to be described later, then one can safely increase the dose.

It is customary to administer the calculated digitalizing dose over a 24-hour period in divided doses, carefully noting the effect of the previ-

ous doses before giving the new one. The calculated dose can be divided in whatever way is most convenient, e.g., into quarters and administered in equal doses every six hours. My preference, however, is to use a larger dose initially and to give the remainder in smaller increments at regular intervals during the next 24 hours or less. The chief advantage of starting with a small dose, such as a quarter of the total dose, is to make sure that there are no toxic effects from the drug. Actually, when purified glycosides are used, one does not need to worry about toxicity at the beginning of digitalization; it is the last quarter of the calculated dose that is much more likely to cause trouble. The advantage of starting with a larger dose initially is that the patient in cardiac failure derives benefits from the medication earlier and that there is little risk of toxicity when the last portions of the calculated dose are given in small increments. Any of the following digitalizing schemes can be recommended as both safe and effective:

TABLE 40. *Digitalizing Schedule*

INITIAL DOSE	REST OF DIGITALIZING DOSE
1/2 calculated total dose	1/4, 1/8 and 1/8 at 4–6 hourly intervals
2/3 calculated total dose	1/6 and 1/6 at 4–6 hourly intervals
3/4 calculated total dose	1/8 and 1/8 at 4–6 hourly intervals

Once full digitalization is accomplished, daily maintenance therapy is begun. For digitoxin, the usual maintenance dose varies from one tenth to two tenths of the total dose required for digitalization, with the lower dose to be tried first. For Digoxin, the daily maintenance dose is usually two tenths of the digitalizing dose. The maintenance amount is ordinarily given as a single daily dose. However, for some patients on Digoxin therapy stability of digitalization seems better maintained by two divided doses daily. Just as for digitalization itself, the lowest dose that is effective is the safest and should be tried first, but there should be no hesitancy in using a larger dose if the patient fails to maintain improvement on a lower one. In adjusting the maintenance dose, each day's dose may be adjusted upward, or twice the usual maintenance dose may be given on one, two or three days during the week or on alternate days. When tablet forms are used, the latter plan is the simpler.

An easy and safe way to regulate the maintenance dose for infants and young children is to use digitoxin scored tablets in 0.05-mg. sizes that can be halved or quartered by the mother. This yields a variety of sizes to provide the appropriate maintenance dose. Each tablet is taken before the next is cut. In this way a standard yet flexible and safe preparation is available. The tablet is crushed, mixed with a small portion of water, milk or food and given at a regular, convenient time each day, usually before breakfast. Digoxin Pediatric Elixir offers a similar

advantage. As the baby grows older the maintenance dose may need to be revised upward to keep pace with the doubling or trebling weight.

When the various digitalis preparations are prescribed, one must be quite sure that the intended preparation is given and that the decimal point is in the proper place. The names of some of the preparations are similar and thus confusing. To pharmacists, nurses or physicians accustomed to adult-size doses, the tiny amounts needed by an infant in failure may seem unreasonable. Moving over a decimal point under such circumstances or in haste must be guarded against.

Unless there are special reasons for doing otherwise, administration of the digitalizing dose is commonly by mouth. Digitoxin is completely absorbed and is well tolerated after oral ingestion; though this information is somewhat less certain for Digoxin, it, too, is quickly effective by the oral route. Preparations for intravenous or intramuscular injection are available for both these drugs if the patient cannot take the medicine by mouth. For digitoxin the parenteral dose is the same as the oral dose; this is assumed to be the case for Digoxin too.

The goal of digitalis therapy is to achieve a therapeutic effect before a toxic effect is reached. Therapeutic efficacy is assessed clinically: by decrease in tachycardia, decrease in size of the liver, disappearance of edema or rales, improvement in heart size and abolition of gallop rhythm, and improvement in well-being of the patient.

There is no direct electrocardiographic correlation to this clinical improvement; instead, the electrocardiogram is a better guide to digitalis toxicity. At the time the patient is improved the only change in the electrocardiogram may be a slowing of the rate. The most frequent change attributable specifically to digitalis is shortening of the Q-T interval, followed by reversal of polarity of the T waves (usually from positive to negative in V_5 and V_6 and the related limb leads) and depression of S-T segments. Increase in atrioventricular conduction time, as measured by the P-R interval, is less common. It is to be noted that these changes are *effects* of digitalis on the heart and in the electrocardiogram and not *toxic* effects of the drug.

Toxic manifestations of digitalis on the electrocardiogram are ventricular premature beats, sometimes multifocal or coupled with regular beats, or in series; atrial paroxysmal tachycardia or atrial fibrillation; sinus pacemaker depression; and conduction disturbances with dropped beats or complete atrioventricular dissociation. These are indications for prompt withholding of subsequent doses until the changes disappear, and then reinstating therapy at a lower dosage level. Since hypokalemia increases the toxic effects of digitalis, the patient's serum potassium level should be checked if the electrocardiographic finding is a serious one and if there is enough time to check it. Potassium chloride can then be administered if renal function is adequate.

Toxic effects of overdosage with digitalis, other than electrocardiographic ones, consist in nausea, vomiting and diarrhea. Yellow vision is rarely complained of by children. Congestive cardiac failure can be produced by large overdosage of digitalis. With purified glycosides these toxic manifestations are unusual. I cannot recall a single instance during the past 10 years that was not due to accidental overdosage of the drug. Toxicity did not occur at the effective therapeutic level in the dosage recommended.

Digitoxin is a very useful preparation. It is fully and regularly absorbed by mouth within four to six hours, and it is slowly excreted over a period of two to three weeks. This implies that if one is careful not to use too large doses that lead to toxicity, this preparation is predictably effective for long-term digitalization as well as short-term usage. Beginning digitalizing doses for the different age groups are as follows:

TABLE 41. *Digitalizing Doses of Digitoxin*

Under 1 year	0.035–0.04 mg./kg./24 hours
1–2 years	0.03–0.035 mg./kg./24 hours
Over 2 years	0.025–0.03 mg./kg./24 hours

The daily maintenance dose starts at one tenth of the digitalizing dose. In some patients revision upward to as much as two tenths of that dose is necessary.

Digoxin is also a purified glycoside, well absorbed by mouth, with a rapid onset of action and with more rapid excretion than digitoxin. Maximal effect of an ingested dose can be expected in three to six hours; the effect is gone in three to six days. The rapid excretion is responsible for its greatest therapeutic merit (that if toxic levels are reached, the effect is not long-lasting) and at the same time for its chief drawback (that stability of digitalization may be more difficult to achieve than with longer-acting agents, and two doses a day may be needed). An elixir of Digoxin is available as a convenient form for pediatric usage. The total digitalizing dose and the maintenance dose are approximately twice that for digitoxin.

Intravenous *lanatoside C* is recommended for emergency situations in which there is no time to lose, as in a newborn infant with congestive cardiac failure from paroxysmal supraventricular tachycardia of a day's duration, or a baby in cardiac failure and with signs of shock, as often happens in endocardial fibroelastosis. An electrocardiogram should be obtained while an intravenous infusion with a three-way stopcock is quickly started. The measured dose of lanatoside C is drawn up and is given through the stopcock into the patient. For accuracy in measurement of small amounts, the drug can first be diluted 1:5 or 1:10. The infusion continues to run slowly so that additional doses can be given

if indicated at 30- to 60-minute intervals. The electrocardiogram and the patient's condition are both observed closely.

An initial dose of 0.025 to 0.035 mg. per kilogram can be given without of fear of toxicity. This amount often suffices to convert a supraventricular tachycardia to normal sinus rhythm or to cause prompt improvement in the patient in serious cardiac failure from other causes. If the desired effect has not been achieved after 30 minutes, additional smaller doses can be given in increments every half-hour to make a total of 0.06 to 0.08 mg. per kilogram in 4 to 6 hours if necessary. The patient is usually clearly improved before the highest of these figures is reached.

Lanatoside C is not only quick acting, but also quickly excreted: a good portion by 12 hours and most of it by 24 to 48 hours. This means

TABLE 42. *Digitalis Preparations for Pediatric Use*

AGENT	PROPRIETARY NAME	PEDIATRIC DOSAGE FORMS	
		Oral	Injectable
Digitoxin....	Crystodigin (Lilly)	Scored tablets: 0.05 and 0.1 mg.	0.2 mg./cc.
	Purodigin (Wyeth)	Scored tablets: 0.05 and 0.1 mg.	0.2mg./cc.
	Digitaline nativelle (Varick)	Tablets: 0.1 mg.	0.2 mg./cc.
Digoxin....	Lanoxin (Burroughs)	Pediatric elixir: 0.05 mg./cc. Scored tablets: 0.25 mg.	0.5 mg. in 2 cc.
Lanatoside C....	Cedilanid-D (Sandoz)	(Not well absorbed)	0.4 mg. in 2 cc.

that for continuation of digitalis therapy the patient will need to be redigitalized with a longer-acting agent. In order for an effective level of digitalis to be maintained without danger of toxicity, the new preparation is administered in divided doses so that its level is being steadily built up as lanatoside C is being eliminated. A convenient plan is to calculate the digitalizing dose of the new drug, based on the amount of lanatoside C required. For digitoxin the digitalizing dose is an equivalent amount, and for Digoxin, about double the amount. The total digitalizing dose is then given in quarters every 6 hours, beginning about 12 hours after the initial dose of lanatoside C. As for all methods of digitalization, it is important to check the patient before the next dose is given. After redigitalization daily maintenance therapy with the second drug begins the next day.

The summary (Table 42) of these three drugs with commercial names and the forms for pediatric use is meant to be helpful to physicians and is not intended as a "plug" for any drug company!

The more detailed account of these most commonly used purified glycosides is not to deny the merit of other digitalis preparations: e.g.,

strophanthin and ouabain for rapid action intravenously and digitalis leaf or Digalen for more leisurely digitalization and maintenance therapy.

Diuretics

Diuretics are the other most helpful group of drugs for use along with digitalis in the treatment of congestive circulatory failure. Some patients in mild or early failure may improve sufficiently with digitalization and ancillary measures so that diuretics are not needed. But for patients sicker than this the use of diuretics during the initial treatment of cardiac failure and sometimes for protracted periods has much to offer. The most important in this category are the mercurial diuretics and the more recently available oral preparation, chlorothiazide.

Mercurial diuretics enter the renal tubular cells, where they block reabsorption of chloride and secondarily of sodium accompanying chloride; as a further consequence they block the reabsorption of water, since the osmotic concentration of sodium chloride becomes high in the tubular urine. There results a diuresis, with a reduction in extracellular fluid from the blood vessels as well as the tissues. Circulating blood volume returns toward normal, and edema disappears. Improvement in the patient accompanies the weight loss of an effective diuresis.

Meralluride (Mercuhydrin [Lakeside]) is one of the best drugs in this group. It is given intramuscularly early in the morning, for the diuresis is greatest in the first 12 hours. The dose can be repeated on the second and third days with a lapse of two or three days before the next dose, to prevent accumulation of mercury.

A suggested starting starting dose for infants in the first few months is 0.1 cc. a day; for older infants, 0.25 cc.; and for older children, 0.5 cc. a day.

This drug may be needed only a few times in the initial management of a patient in failure; thereafter the improvement persists simply from the use of maintenance digitalis and salt restriction. Other patients with more serious forms of heart disease with cardiac failure may need the continued intermittent use of Mercuhydrin or another diuretic at intervals of once a month to twice a week or more.

A new oral diuretic, chlorothiazide (Diuril [Merck Sharpe & Dohme]), is now available. It affects the renal transport of electrolytes in such a way that large quantities of sodium and of chloride and lesser amounts of potassium and bicarbonate are excreted. Water loss is commensurate with the increased electrolyte output. This drug is well absorbed from the gastrointestinal tract and produces a diuresis that begins after about 2 hours and lasts for 6 to 12 hours. One or two doses a day, one early in the morning and the next six hours later, can be given to cause a

diuresis during the daytime and permit a restful night. The drug can be used in this fashion for several days until edema disappears. It is particularly useful for those patients who continue to need diuretics. Its advantage as an oral preparation is evident: "no more needles!" and no need for a house call or hospital visit for an injection. Furthermore, there is less disturbance of electrolyte balance than with the long-term use of mercurials. Except for occasional vomiting at high doses, no toxic effects have been reported. In hypertensive patients it lowers blood pressure and may be advantageous in treatment of children with chronic renal disease and cardiac failure.

Pediatric dosage schedules are not yet thoroughly worked out; the dose for each patient must be adjusted as to size and frequency. The smallest dose and longest interval between doses that will produce a diuresis and maintain an edema-free state is the aim. Approximately 25 mg. per kilogram as a single dose or in 2 or 3 divided doses a day has been suggested by the manufacturers as a reasonable dose for pediatric usage, but we have obtained satisfactory diuresis on much smaller doses than this (as little as 10 mg. per kilogram) and would suggest starting at a lower level, increasing as necessary. The interval between doses may also be varied for maintenance therapy: e.g., once or twice a week, or alternating two days in a row and two or three days without this medication, basing the frequency on the patient's response.

In some patients with serious heart disease who have received diuretics (particularly mercurials, but also chlorothiazide) for prolonged periods, the edema becomes refractory to treatment. This is because of a disturbance in electrolyte and fluid balance. With mercurial diuretics there is a proportionally greater loss of chloride than of bicarbonate from extracellular fluid, so that a hypochloremic alkalosis results. If the patient has adhered to a low salt diet, but has had little or no fluid restriction, the electrolytes present are diluted by the large volume of water. Serum electrolyte concentrations will be low, sometimes with equal depression of sodium and of chloride, but more often with greater depression of the chloride. This situation is referred to as the "dilution syndrome" or "low-salt syndrome." Since the action of mercurials is dependent on the presence of chloride ion in moderate amount, the drug is ineffectual when chloride is low.

Chemically, this condition can be corrected by an acidifying regimen designed to elevate blood and urine chloride. Rubin and his collaborators have used in combination two agents, one a carbonic anhydrase inhibitor, Diamox, and the other a compound such as ammonium chloride which supplies chloride ion. Each of these has a weak diuretic effect alone, but their use together restores the patient's response to mercurial diuretics. Diamox favors renal excretion of sodium; the other agent provides chloride ions in excess so that a controlled hyperchloremic

acidosis is produced. When the urinary chloride level has risen to 40 to 50 mEq. per liter, usually after 3 or 4 days of this combination, administration of mercurials will be followed by a diuresis once more. The difficulty is that the few patients in the pediatric age group in whom this therapy has been used have had such serious heart disease (such as cardiac failure associated with hemochromatosis in severe, chronic anemia) that improvement has been only temporary.

Salt Restriction

Salt restriction is a third valuable tool in the therapy of congestive failure. When renal tubular reabsorption of sodium is excessive in cardiac failure, it is reasonable to reduce the load delivered to the kidneys by reducing the intake. A powdered milk preparation low in salt (Lonolac [Mead Johnson]) is an aid in this direction for babies, and some dairies prepare a low-salt milk. Commercially available strained baby foods contain little salt, and for those old enough to eat table fare, it is simple for the mother to refrain from salting the food during cooking. Salt restriction more stringent than this is seldom needed. Babies object not at all, and most children become adjusted to the new taste. A wide range of foods is possible, and many kinds of spices and herbs can be used for greater palatability.

Moderate restriction of sodium is advisable during the initial therapy of patients in cardiac failure. After the patient has maintained improvement, a more liberal salt intake can be tried; many require no further salt restriction.

Fluid Restriction

Fluid restriction of slight to moderate degree is advantageous in limiting reaccumulation of edema, but fluids need not be restricted so much that the child is thirsty. It is more a question of limiting the excessive intake of fluids. For infants in failure this problem seldom arises; more often the trouble is to get the sick infant to take enough to grow. When fluids for the older child are limited to 1000 cc. daily, and the intake measured, it is interesting to see how few of them voluntarily drink even this much when under treatment for cardiac failure.

Bed Rest

Rest in bed is important for the failing heart. Generally infants and children are wise in this regard: they do not feel like doing much when cardiac failure is manifest; so they rest. It is usually a good sign when they start to be active again.

Oxygen Therapy

Oxygen therapy relieves those in respiratory distress. It may quickly be discontinued when the improvement is prompt, but some patients need it for long periods. The drying effect of oxygen can be avoided by proper humidification.

Position

The orthopneic position for patients with pulmonary congestion makes them more comfortable. It is hard to keep little babies in this position with head and chest elevated; they keep sliding down. Small bedrolls at strategic locations help the baby stay semi-upright at least part of the time. Older children quickly make their preferences for a semi-upright position known.

Treatment of Respiratory Infections

Treatment of respiratory infections is an adjunct to therapy. Even a mild respiratory infection may make the difference between adequate cardiac compensation and cardiac failure. Especially in those babies with flooded lung fields due to their congenital anomaly, the differential diagnosis between cardiac failure and bronchopneumonia clinically and radiographically may be difficult. When in doubt, the safest therapy is treatment for both conditions.

Morphine

Morphine, 1 mg. per 5 kg., is beneficial when there is acute pulmonary edema.

Ancillary Treatment

Ancillary treatment such as sedation, laxatives, and so on, is used as indicated to make the patient more comfortable.

Treatment of Specific Causes of Cardiac Failure

Treatment of the underlying condition is equally important as therapy of the congestive circulatory failure. Certain cardiac malformations amenable to surgery should be operated upon as soon as the cardiac failure is under control. These include patent ductus arteriosus, pulmonic stenosis with intact ventricular septum, and aortic stenosis. For other conditions, such as infants with large ventricular septal defects or coarctation of the aorta, there is a greater chance for successful out-

come if operation is deferred till the patient is older. For these a trial on intensive medical management of the cardiac status is advisable after correction of the failure.

Appropriate therapy for conditions such as hyperthyroidism and some of the anemias can eliminate the burden on the heart. Supportive therapy for patients with acute nephritis or myocarditis helps tide these patients over, once circulatory failure is controlled, until the illness spontaneously subsides. When rheumatic carditis is recognized early and treated with hormones, the carditis can be stopped. With continuing medical and surgical advances there is reason to hope that, for many more, the underlying condition which initiated cardiac decompensation will be correctable. Until that time the measures described above should control the congestive circulatory failure.

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525 East 68th Street
New York 21, New York

COMPLICATIONS OF FLUID THERAPY IN PATIENTS WITH NEUROLOGIC DISEASE

With Special Emphasis on Water Intoxication and Hypertonic Dehydration

JOHN D. CRAWFORD, M.D.

PHILIP R. DODGE, M.D.

Water intoxication and hypertonic dehydration are serious complications of improper fluid therapy. Recognition of these complications is of immediate, practical importance, for a failure to recognize them may result in death or permanent disability. A particular hazard to the neurologic patient is created by the fact that the signs of water intoxication and hypertonic dehydration are in themselves neurologic. Thus it may be difficult to distinguish the presence of the therapeutic complication from the primary illness.

In this paper some of the physiologic processes underlying water intoxication and hypertonic dehydration as they pertain to the nervous system and its function will be reviewed. Secondly, in order to clarify some of the clinical manifestations of the syndromes in uncomplicated

From the Department of Pediatrics and Neurology, Harvard Medical School, and the Children's Medical and Neurology Services, Massachusetts General Hospital, Boston.

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form, three cases of water intoxication occurring in the absence of primary neurologic disease will be described. Subsequently, a number of illustrative cases will be discussed in which water intoxication or hypertonic dehydration resulted from improper fluid therapy in patients with a variety of underlying neurologic disorders. Each case illustrates one or more error in management. Finally, we will consider the case history of a child in whom signs and symptoms were ascribed initially to a disorder of water and electrolyte metabolism; subsequently it was shown that they could equally well be due to a primary disease of the central nervous system.

PHYSIOLOGIC CONSIDERATIONS

Two basic physiologic principles enter into consideration of fluid therapy as it relates specifically to the central nervous system and its diseases.

First, the brain is enclosed within a relatively nonyielding skull which permits volume changes in one intracranial compartment only at the expense of another. Thus swelling of the brain is of necessity associated with a diminution in volume of blood, cerebrospinal fluid or both. Shrinkage of the brain must, on the other hand, result in expansion of blood or cerebrospinal fluid compartments. In infants the open sutures give unusual flexibility to the system. Enlargement of the skull due to separation of the sutures may be seen with brain swelling. Reduced skull size and overriding of sutures occur with brain shrinkage as in cases of hypertonic dehydration.

Secondly, free exchange of electrolytes and other nonaqueous substances between the blood and the cerebrospinal fluid is limited by the so-called blood-brain barrier. Conversely, water appears to flow rapidly and freely in and out of cerebrospinal fluid, brain and blood. For example, acute changes in brain water per unit of dry solid up to 20 per cent have been induced in experimental animals over a 3-hour period, whereas changes in electrolytes against the same denominator are minimal.[4]

In the state of hyperosmolality of body fluids resulting from loss of water out of proportion to electrolytes, whatever the basic disease process, the brain shrinks. Secondarily, there is a compensatory expansion of the intracranial blood volume and probably of the cerebrospinal fluid space as well. In the state of hypotonicity of extracellular fluids there is swelling of the brain and reduction of the intracranial blood and cerebrospinal fluid volumes. If the changes in either direction are excessive, dysfunction of the central nervous system results. Curiously, the symptoms are similar in hypertonic dehydration and the hypotonic state which is often termed water intoxication. Irritability, restlessness, stupor, coma and seizures are common to both conditions, and focal neurologic signs are unusual. Meningeal signs are frequently observed in infants

with hypertonic dehydration, but absent in those with water intoxication (personal communication from Lewis A. Barness). There are other differences which appear to be the consequence of changes in intracranial pressure rather than of the metabolic disturbances per se.

In severe hyperosmolality there may be a striking reduction of cerebrospinal fluid pressure. The clinical and experimental studies of Luttrell and Finberg[17] demonstrate a remarkable dilatation of vessels in association with the shrinkage of the brain. This, in all probability, accounts for the tiny subarachnoid and brain hemorrhages which appear to result from rupture of small vessels. Tearing of the veins traversing the subdural space may account for some of the subdural hemorrhages occasionally seen. Nevertheless in most instances intracranial bleeding does not explain the neurologic signs, although it may compound the clinical problem. The reason for the primary cerebral dysfunction in the hyperosmolality syndrome is unknown, but is presumably related to an abnormality of function at the cellular level.

In water intoxication an increase in the cerebrospinal fluid pressure is seen which, if extreme, may result in herniation of the brain at either the incisura of the tentorium or at the foramen magnum. Compression of vital brain stem centers producing decerebration, hypertension, respiratory failure and death may be the consequence. However, here, as in hypertonic dehydration, the effects produced by changes in pressure are of secondary importance in the production of the clinical neurologic syndrome. In rabbits mechanical elevation of the cerebrospinal fluid pressure fails to produce the electroencephalographic changes of water intoxication. Furthermore, maintenance of normal pressure during induction of experimental water intoxication does not prevent the syndrome.[4] Dysfunction of the nervous system can be related in these animals to brain swelling and, in particular, to expansion of its intracellular compartment. Treatment with hypertonic solutions of varying chemical composition (3 per cent sodium chloride, 15 per cent mannitol or 6 per cent urea with 5 per cent dextrose) results in a reduction in the brain water, the intracellular space diminishing in volume somewhat more than the extracellular space. The clinical neurologic syndrome also has been shown to be unrelated to either hyponatremia or hypochloremia in any direct sense,[4] for, when hypertonic mannitol is infused in treatment of water intoxication, the serum water-solute ratio is immediately lowered in the direction of normal, and dramatic improvement in clinical symptoms and the electroencephalogram rapidly follows. This is in spite of the fact that the infusion of mannitol results initially in a further lowering of the serum sodium and chloride concentrations.

CLINICAL CONSIDERATIONS

CASE I.* A 12-year-old girl was admitted to the hospital with acute appendicitis. The illness was of brief duration, and vomiting had not occurred. There were no neurologic symptoms. After a short period of observation she underwent appendectomy. Preoperative medication included 4 mg. of morphine and 0.3 mg. of atropine. After surgery she was given 50 mg. of Demerol to be readministered at 3-hourly intervals as necessary for pain. Before, during and after operation she was given intravenously a multiple electrolyte solution† with 5 per cent dextrose at the rate of 3 liters per square meter per day.

Fifteen hours after operation she complained of increasing headache, for which Demerol was given twice at 3-hour intervals. Eleven hours after the last dose of Demerol the patient was found convulsing. She was treated with 150 mg. of sodium amytal, intravenously, and 4 ml. of paraldehyde by rectum, and the fits ceased. However, she remained poorly responsive, whimpered and rolled about restlessly in bed. The neck resisted anterior flexion. She had tonic neck reflexes and bilateral Babinski signs. Optic fundi were negative. There were no Chvostek or Trousseau signs. The cerebrospinal fluid was under an initial pressure of 450 mm. of water with a total protein content of 25 mg. per 100 ml.

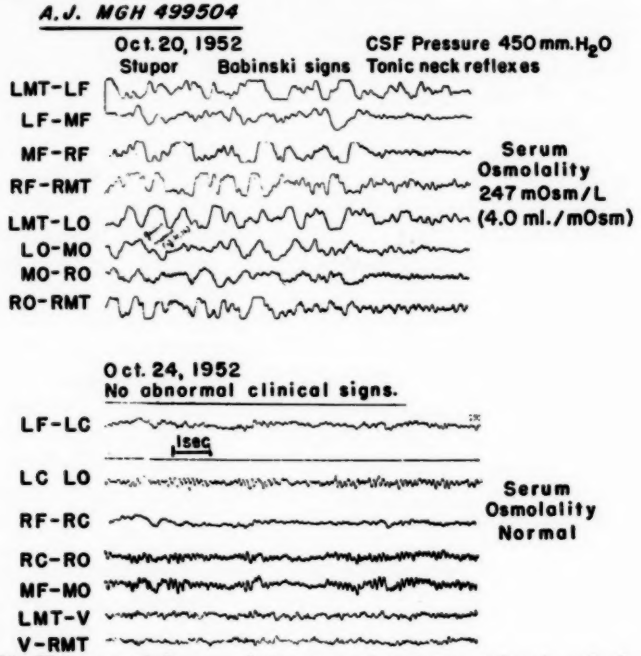

Fig. 31. Electroencephalograms during water intoxication (above) and after recovery (below) (case I).

* Certain aspects of this case have been reported previously.[10]

† Sodium, 40 mEq. per liter; potassium, 35 mEq.; chloride, 40 mEq.; phosphate, 15 mEq.; and lactate, 20 mEq. per liter.

The electroencephalogram showed bursts of high voltage delta activity interspersed with more normal alpha and beta rhythms (Fig. 31). A diagnosis of acute toxic encephalopathy was suggested by the neurologic consultant, but the correct diagnosis was established when the serum water-solute ratio was found to be 4.0 ml. per milliosmol, the upper limit of normal being 3.7. The same serum sample showed the sodium to be 120, chloride 79 and potassium 4.8 mEq. per liter. Urine was paradoxically concentrated with a water-solute ratio of 1.8 ml. per milliosmol. Intravenous fluids were discontinued.

Diuresis occurred, and clinical recovery was complete within 24 hours, at which time serum electrolyte values were normal. Two days later the electroencephalogram was repeated and was also normal.

Figure 32 gives some additional details of the patient's course. At the bottom, in section *C*, the rate of parenteral fluid infusion is shown against a shaded zone indicated as the normal range of physiologic tolerance. The latter is a function of the ability of the kidney normally to form urine ranging from high dilution in which the water-solute ratio or "water concentration" may be 10 ml. per milliosmol to extreme concentration in which the water-solute ratio falls to approximately 1 ml. per milliosmol (see section *B*).* By considering this range of kidney adjustment and making an estimate of the expected urinary solute excretion, the extent of normal physiologic tolerance shown in section *C* is easily computed.† In this frame of reference the rate of infusion actually given the patient, shown by the horizontal line, appears quite safe.

The water-solute ratio of urine actually formed by the patient is given by the heavy line in section B. The broken line above indicates the urine water concentration required to prevent water retention from the fluid administered. Evidently the patient failed to make the appropriate homeostatic adjustment necessary to eliminate water in excess of bodily needs. Some of the factors responsible for the continued production of urine of low water concentration in the face of the rising serum water and falling serum sodium concentrations (section A) are shown by the notations above. Ether anesthesia, morphine and Demerol are all potent antidiuretic substances.[1, 10] These were the agents responsible for the patient's inability to adapt normally to a fluid intake which otherwise would have been comfortably tolerated. The convulsions beginning at the arrow culminated the clinical picture of water intoxication, of which

* It is to be noted that the "water-solute ratio" or "water concentration" of a fluid-like serum or urine is the reciprocal of the value for effective total osmolality.

† For instance, in this patient the lowest rate of parenteral fluid administration compatible with maintenance of water balance can be computed as follows: Insensible water loss would amount to 1 liter per square meter per day. Since oxidation of fat and carbohydrate yields about 200 ml. of water per square meter per day, this amount may be subtracted from the above figure, yielding a residual of 800 ml. which must be supplied in addition to the least amount necessary for urine formation. Solutes requiring excretion in the urine will be derived from the electrolytes (omitting lactate, which is metabolized to carbon dioxide and water) contained in the infusion (130 milliosmols per liter) and from urea derived endogenously (approximately 100 milliosmols per square meter per 24 hours). The least volume of urine sufficient for excretion of the solute load will be the product of the sum of these 2 components and the water-solute ratio value for maximally concentrated urine, 1.0 ml. per milliosmol. These considerations yield a minimum figure for this particular parenteral fluid of 1 liter per square meter per 24 hours. Maximum tolerance depends on the same considerations with respect to insensible loss and water of oxidation. The figure for the upper limit of the water-solute ratio of urine (10 ml. per milliosmol) is now applicable. It must also be kept in mind that with delivery of larger volumes of the parenteral fluid, the solutes derived therefrom will be proportionately increased. From these considerations alone a large tolerance is indicated. However, the lesser figure of 6 liters per square meter per day shown in the chart depends on the further consideration that acute loads of sodium greater than about 250 mEq. per square meter per day are likely to lead to unphysiologic retention. Six liters of the particular parenteral fluid solution used here would deliver 240 mEq. of sodium and 210 mEq. of potassium.[28]

headache had been the first symptom. Intravenous fluids were discontinued. The erratic upward course of the line for urine water concentration in section *B* indicates incomplete urine collections in this period. Note, however, that a full renal adaptive response was not reached until 18 hours after the last Demerol dose.

Comment. In this patient, who had neither underlying central nervous system nor metabolic disease, fluids of the type and in the amounts given would normally have been well tolerated. However, water intoxication developed as a consequence of an error in clinical judgment. The physicians in charge failed to take cognizance of the temporary loss of two of the body's homeostatic capacities occasioned by the anesthesia

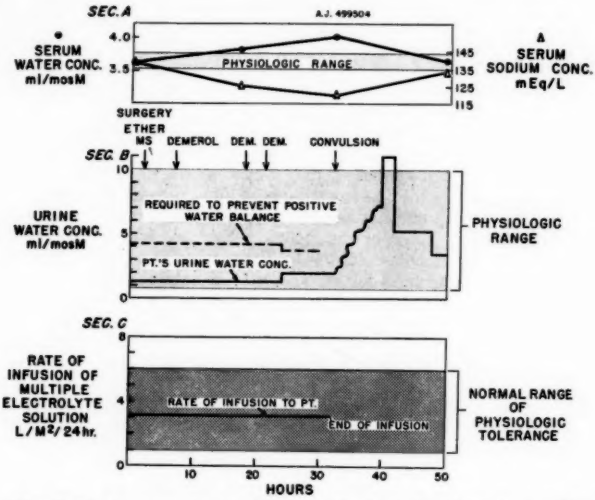

Fig. 32. Metabolic consequence of ether anesthesia and opiates in a patient undergoing appendectomy (case I).

and opiates. First, ether anesthesia and opiates interfered with the patient's ability to produce dilute urine, and, secondly, the "thirst" mechanism, which ordinarily makes oral fluids abhorrent in the face of a fluid surplus, was short-circuited by the parenteral therapy. A further error in judgment involved the administration of Demerol for headache, an early symptom of water intoxication. The antidiuretic effect of this drug delayed the return of normal ability to dilute the urine.

In retrospect it is evident that, in addition to the complaint of headache, there were a number of other clues to the developing water intoxication that were overlooked. Actually, all the necessary data were available, but, as often happens, their significance was lost in a tabular record. A graphic chart of fluid balance would have revealed water

retention which could have been verified by weight gain. The chances of detecting impending trouble are materially increased by this method of charting. Also, had the patient been carefully examined at the time when she was complaining so bitterly of headache, confusion and impaired awareness and responsiveness would have been noted. Older children and adults have keen insight into their inability to think quickly or accurately during the early stages of this disturbance.

On the average, a fluid allotment of 1.0 to 1.2 liters per square meter per day, or, put differently, the least amount compatible with maintenance of water and electrolyte balance, should be used throughout periods when pharmacologic agents are active in inhibiting normal dilution of urine. The composition of the fluid given this patient should not be indicted, for, in the correct amounts, experience has proved it safe in several hundred patients undergoing surgery in some of whom detailed metabolic balance studies are available.[2, 25]

CASE II. A 15-month-old boy with an esophageal stricture secondary to neonatal repair of a tracheo-esophageal fistula underwent retrograde bouginage through a gastrostomy opening. He was prepared with 0.6 mg. of morphine sulfate and 0.2 mg. of atropine and received ether anesthesia. Two hours after the start of anesthesia he coughed, became apneic and had noisy respirations associated with unresponsiveness and asynchronous, generalized convulsive twitchings of arms and legs. There were irregular, spasmodic contractions of the diaphragm necessitating artificial ventilation for more than 2 hours. He was poorly responsive, with periorbital edema, and was convulsing intermittently. The diagnosis of water intoxication was considered by consulting physicians, but, when inquiry was made about administration of parenteral fluids, it was reported that none had been given. The seizures terminated after 30 mg. of intravenous sodium amytal.

Two hours later, seizures recurred, and it was then learned that during the bouginage procedure tap water had been instilled into the stomach for the purpose of distending it for endoscopy. It was noted that reflux from the gastrostomy had necessitated use of approximately 4 liters. A clinical diagnosis of water intoxication was made and confirmed by the finding of a serum water-solute ratio of 3.9 ml. per milliosmol, and sodium of 124 mEq. per liter. Over the next half hour approximately 50 mEq. of sodium were administered in the form of hypertonic (3 per cent) sodium chloride. There was dramatic improvement. Seizures ceased, breathing became regular, and the infant responsive. Thirty minutes later, however, after an additional 50 mEq. of sodium in hypertonic solution had been given, laryngeal stridor and carpopedal spasm developed, suggesting a diagnosis of tetany. This cleared within minutes after 1.0 gm. of calcium chloride had been given through the gastrostomy tube. No further specific treatment was necessary. Diuresis was copious over the next several hours, and by the following day the patient had recovered from the episode. At this time the serum water-solute ratio was 3.7 ml. per milliosmol.

Comment. One is prone to forget that homeostasis is served not only by mechanisms governing excretion, but also by those which govern intake such as thirst, hunger and salt-craving.[20] Hence it is unusual to encounter water intoxication following voluntary ingestion of oral fluids, though occurrence in this manner has been recorded.[22] As commented earlier, when fluid is given by parenteral infusion or, as in this case, is introduced into a body cavity where it becomes available for

absorption, the "thirst" mechanism is circumvented and has no opportunity to afford its usual protection. Thus it is important to avoid use of hypotonic fluids for endoscopic procedures and to use instead isotonic solutions of saline, mannitol or glycine, for example.

The form of the convulsive twitchings observed in this case is entirely typical of that seen in the metabolic encephalopathies. Control by barbiturates is usual, and the response to treatment should not militate against the diagnosis.

The occurrence of tetany complicating treatment with hypertonic saline deserves comment. Symptomatic hypocalcemia is seen in hypernatremic dehydration and has been studied experimentally by Finberg and Fleishman.[7] Though the exact mechanism of its production remains obscure, it can be precipitated by administration of hypertonic saline as in the present case, prevented by concomitant potassium intake, and is responsive to treatment with calcium compounds given intravenously or, as here, delivered into the stomach. When it is suspected clinically, the diagnosis can be rapidly confirmed electrocardiographically by the finding of an abnormal prolongation of the Q-T interval.

CASE III. A 2½-year-old boy without prior history of seizures was referred from another hospital with bilateral bronchopneumonia and status epilepticus which followed the parenteral administration of 2100 ml. of fluid over a 17-hour period. This represented an intake of 4400 ml. per square meter per day, two thirds of which was 5 per cent dextrose in water administered by hypodermoclysis, the remainder, normal saline given intravenously. Generalized convulsions began 10 hours prior to transfer and continued intermittently despite treatment with 100 mg. of phenobarbital and 4 mg. of morphine sulfate. Convulsions were finally controlled with ether.

On admission to the hospital rectal temperature was 100.0° F., pulse 110 and blood pressure 110/70. He was pale, but not cyanotic. There was periorbital and scrotal edema. Coarse rhonchi were heard throughout both lungs, and bilateral bronchopneumonia was demonstrated on chest radiograph. There was no response to command or to painful stimuli, but the arms showed occasional spontaneous movements. Tendon reflexes were absent and the plantar reflexes extensor. The ophthalmic veins appeared distended, and there was a small hemorrhage adjacent to the right optic disk.

The diagnosis was uncertain at this point. A lumbar puncture was done to exclude meningitis. The initial pressure was 420 mm. of water; the fluid was clear and contained 5 lymphocytes. The serum chemical analyses were reported shortly thereafter and the diagnosis of water intoxication established by a serum water-solute ratio of 4.5 ml. per milliosmol. The serum sodium was 110, chloride 67, potassium 2.9, and magnesium 4.1 mEq. per liter. The sugar was 236, nonprotein nitrogen 20, calcium 9.2 and phosphorus 4.6 mg. per 100 ml. The serum total protein was 5.9 gm. per 100 ml. The pH of venous blood was 7.47 and the carbon dioxide content 23 mEq. per liter. The peripheral blood contained 8200 white blood cells per cubic millimeter. Hemoglobin was 10.8 gm. per 100 ml. The urine was paradoxically concentrated with a specific gravity of 1.022.

Treatment with 3 per cent saline was started shortly after admission. Over the next several hours there was progressive improvement in awareness and responsiveness, and seizures did not recur. During recovery, if disturbed, the legs became rigid in extension, and grossly ataxic movements of the right arm developed. The left arm was secured for intravenous therapy and was not evaluated. The Babinski signs persisted over the first 5 hours of treatment. Before the end of this time the boy could be roused and

said "Mama" and "Daddy." His serum water-solute ratio had fallen from 4.5 to 4.2 ml. per milliosmol, while the sodium had risen to 121, chloride to 82 and potassium to 3.0 mEq. per liter. The cerebrospinal fluid pressure had fallen to 35 mm. of water.

During the next 2 days the child alternated between what appeared to be deep sleep and fairly normal awareness and responsiveness. Six days after the acute episode he obtained an average score in the nonverbal intelligence tests.

Electroencephalographic records were obtained at intervals throughout the course of treatment and are of sufficient interest to be considered in some detail. The first,

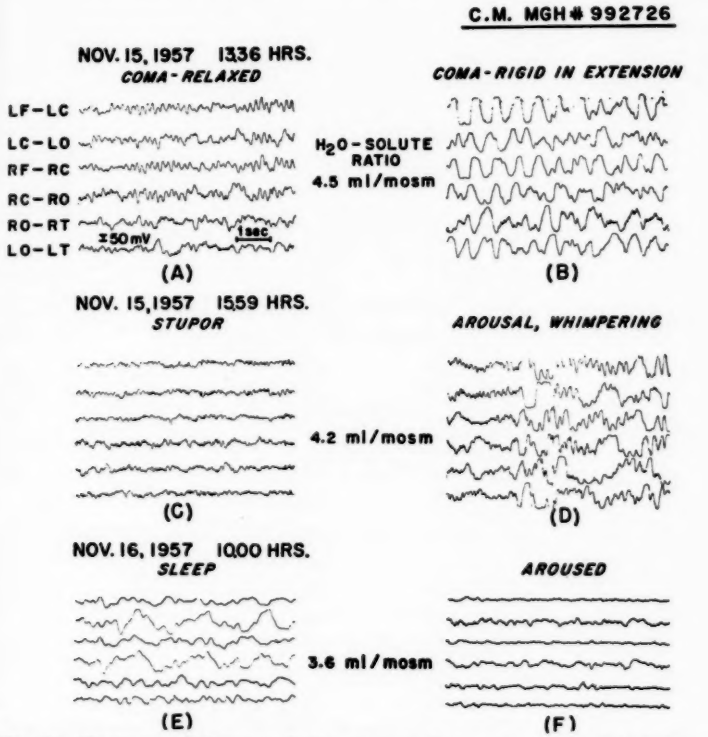

Fig. 33. Electroencephalograms during recovery from severe water intoxication. Those on the left were made when the patient was undisturbed; those on the right moments later after stimulation. The time sequence in recovery is indicated.

taken 2 hours after treatment began, was grossly abnormal and was characterized by a predominance of 6 to 7 per second waves of 50 to 100 microvolts. These waves were more prominent centrally and at the vertex (Fig. 33, *A*). In addition, high voltage delta waves of 1 to 3 per second and of 100 to 200 microvolts appeared diffusely and sporadically in all leads. There were diffuse bilateral, symmetrical bursts of very high voltage 1 to 2 per second waves correlating with the attitude of extensor rigidity which were evoked by painful stimuli (Fig. 33, *B*). Within 4 hours after treatment began there was a more normal electrical response to painful stimuli characterized by about 6 per second activity of high voltages in all leads (Fig. 33, *D*). At this time there was less generalized rigidity, more coordinated movement, whimpering and 1 or 2 clearly articulated verbal responses.

On the second and fourth days of treatment when he was clinically much better there was, paradoxically, more generalized slowing of the electroencephalogram in the resting state (Fig. 33, *E*). When he was aroused, much of this disappeared, and faster frequency lower voltage developed (Fig. 33, *F*). Two months after the episode of water intoxication the electroencephalogram was essentially normal for age.

Comment. The antidiuretic effects of morphine and ether combined with an excessive load of electrolyte-free water to cause water intoxication in this case as in the previous two. Under this circumstance the water intake would have been grossly excessive by any route of administration, but a special problem was created by the hypodermoclysis. Since 5 per cent glucose is isotonic with body fluids, there is no tendency for a subcutaneous depot to draw water from adjacent tissues. But, before water can be absorbed from the depot for general body distribution, sodium and chloride must accumulate until a concentration equilibrium between the depot contents and other interstitial fluid is reached. This redistribution of electrolyte has two potential dangers: Water intoxication may result from loss of electrolyte to the depot, thus elevating the water-solute ratio of other body fluids. Secondly, and this is especially true in an already dehydrated child, loss of extracellular electrolytes to the depot lowers the osmotic pressure of plasma and interstitial fluid. This in turn causes extracellular water to shift intracellularly with resultant edema. Extracellular dehydration is aggravated, and shock may supervene as the intracellular edema develops. An important manifestation of increase in intracellular water is brain swelling with rise in cerebrospinal fluid pressure.

In the present case the increase in intracranial pressure was large and resulted in the retinal hemorrhage, though this is an unusual finding. The decline in cerebrospinal fluid pressure in response to hypertonic fluid was dramatic (from 420 to 35 mm. of water) and comparable to changes observed in experimental studies.[4] It will be recalled (cf. Physiologic Considerations) that in the experimental studies artificial lowering to normal of cerebrospinal fluid pressure in the water-intoxicated animal resulted in neither clinical nor electroencephalographic improvement. In this child clinical improvement did occur and is referable to the fall in the serum water-solute ratio from 4.5 to 4.2 ml. per milliosmol. Although the latter figure is well above that mentioned previously as the level at which symptoms of water intoxication are generally evident, this is a good illustration of the fact that the body responds favorably to a relatively small change if this is in the direction of normal. A useful corollary is that it is generally unnecessary and undesirable in clinical medicine to attempt rapid total restoration of a biochemical abnormality.

The correlation between the clinical and electroencephalographic findings is of particular interest (Fig. 33). The first electroencephalo-

graphic tracing was obtained early in treatment at a time when the patient was poorly responsive and rigid. On casual inspection the electrical disturbances were less severe than anticipated, but on closer scrutiny of the record the relatively normal six to seven per second activity clearly did not arise from the occipital leads where it might pass as normal activity for the age, but was of central origin and very likely from subcortical structures. With arousal the electroencephalogram became considerably worse in appearance, and the very slow generalized delta activity appeared. This form of abnormality has been described previously in encephalopathies by Li, Jasper and Henderson.[16]

It is of further interest that the electroencephalogram remained abnormal for several days after treatment and was associated at times with deep sleep. The data suggest that re-establishment of normal neuronal function in serious disturbances may be delayed after restoration of normal serum concentration values for water and electrolytes. Whether this is due to delay in attaining normal water and electrolyte relationships at the cellular level or to neuronal damage induced by these disturbances is not clear. In one severely water-intoxicated experimental animal an abnormal reduction in voltage persisted several hours after completion of treatment, but was normal the following day.[4]

Case IV. A 3-year-old girl was admitted to another hospital for evaluation of an infantile right hemiparesis. The child could walk and say a few simple words. On examination the left side of the skull was smaller than the right. There was a hemiparesis, hyperreflexia and an extensor plantar response on the right side.

Laboratory studies, including examination of the cerebrospinal fluid, were negative. A pneumoencephalogram with introduction of 45 ml. of air was done under ether anesthesia and demonstrated an enlarged ventricular system with shift of the lateral and third ventricles toward the left side.

After this procedure the child regained consciousness, but vomited repeatedly and was irritable and drowsy. After 1000 ml. of 5 per cent dextrose in water had been given by hypodermoclysis she became less responsive and on the second day after pneumoencephalography began having brief, generalized convulsions. The serum nonprotein nitrogen was 87 mg. per 100 ml. and chloride 68 mEq. per liter. Urine output was limited to 100 ml. in 2 days. Attempts at intravenous therapy were unsuccessful, so that 250 ml. of Ringer's solution were given by proctoclysis.

She became increasingly less responsive, grew decerebrate, and Cheyne-Stokes respirations developed. Terminally, the serum chloride had risen to 85 mEq., but the carbon dioxide content was less than 10 mEq. per liter. The hematocrit level was 45. The cerebrospinal fluid was normal just before death, although the pressure was not measured.

Postmortem Findings. At autopsy the left side of the cerebrum was grossly atrophic; the gyri were reduced in size, and the pattern was difficult to identify. Nevertheless the sulci were prominent, the gyri were rounded, and the cortex was firm on palpation. There was swelling of the hippocampus and the anterior pole of the temporal lobe on the left, but other parts of this hemisphere were uninvolved. The entire right cerebral hemisphere and both cerebellar hemispheres were swollen. The right cerebral hemisphere was shifted byond the midline to the left. The sulci were shallow and the gyri flattened. The left temporal lobe uncus had herniated through the incisura of the tentorium. The specimen is shown in Figure 34.

Comment. The clinical findings and chemical data leave no doubt

as to the diagnosis. Again, a number of common therapeutic errors are illustrated by this case. First, the amount of fluid given, especially in view of the ether anesthesia, was excessive. Moreover, vomiting undoubtedly resulted in electrolyte loss. Such losses accelerate the elevation in the water-solute ratio of body fluids when large volumes of dextrose and water are administered. The special hazards of hypodermoclysis have already received comment.

The oliguria in this patient reflects not only the influence of ether anesthesia, but also renal embarrassment as shown by the elevated nonprotein nitrogen. Diminishing renal blood flow and glomerular filtration rate with increasing oliguria are common features of advanced, uncom-

Fig. 34. Under surface of brain from case IV, demonstrating swelling of all but gliotic portions of the left hemisphere.

plicated water intoxication. The relatively normal hematocrit value is of interest because it emphasizes the fact that an expanded blood volume is not a necessary finding in water intoxication. The syndrome may develop when there are extensive losses of solute with either gain or depletion of body water. This occurs as a result of salt loss through the skin in normal persons and is particularly frequent in patients with pancreatic fibrosis[11] when they are exposed to extreme heat and allowed to drink water ad lib. When water intoxication results from circumstances such as these, it is characterized by clinical signs of dehydration, an elevated water-solute ratio in serum and elevated values for serum total protein, hemoglobin and hematocrit. A second set of circumstances of even greater clinical importance is that encountered in pa-

tients hypoproteinemic owing to previous malnourishment as well as in infants under six months and nephrotics. Here, hypoproteinemia leads to inadequate return of interstitial fluid to the venous end of capillaries. This in turn leads to hypovolemia, which has two important consequences: one is to make the patient thirsty, the other to cause an outpouring of antidiuretic hormone irrespective of the water-solute ratio of the body fluids. As a result, the patient may demand water to drink. Since, however, ingested fluid fails because of the hypoproteinemia to expand vascular volume, thirst is unslaked. Edema develops. Oliguria persists, and water intoxication with a relatively high hematocrit and low serum total protein is the end result.[24] This train of events has recently been encountered in a patient with chronic brain abscess.

Returning to the case at hand, the patient might well have survived had the condition been recognized and hypertonic solutions administered by vein. Inability to puncture a vein, as was the case here, is no excuse for administering fluid by a less effective route. Exposure of a vein by surgery and direct canalization should have been accomplished.

Finally, the distribution of the brain swelling is of interest. It suggests that water exchange between blood and the gliotic, relatively avascular left hemisphere was defective.

CASE V. A 2½-year-old girl was brought to another hospital 7½ hours after an acute episode which had begun with a 15-minute febrile convulsion. She had a history of 3 febrile seizures in the 8 months preceeding admission.

Immediately after the initial seizure she had been given an estimated 300 to 400 ml. of tap water by enema. According to the history, much of the enema was expelled, but she became drowsy, "whiny" and about an hour later had a 30-minute generalized seizure followed by unresponsiveness. The enema was repeated. Again much of the fluid was lost, but a short while later status epilepticus developed which was said to have lasted for 4 hours. During this period she was given 4 or 5 more tap water enemas. An estimated 1500 to 1800 ml. of water was instilled with minimal returns. The abdomen became distended, and vomiting ensued. Just before leaving home she was given 120 mg. of sodium phenobarbital.

On admission to the hospital she was deeply comatose and convulsing intermittently. Temperature was 101.6° F., and there was an exudative tonsillitis. The seizures stopped after 180 mg. each of sodium amytal and sodium pentobarbital were given intravenously.

On lumbar puncture the cerebrospinal fluid was estimated to be under increased pressure, but the patient was not relaxed. The fluid contained 2 lymphocytes and 2 polymorphonuclear leukocytes per cubic millimeter. The protein and sugar concentrations were, respectively, 17 and 65 mg. per 100 ml.

The initial serum sodium concentration was 106, chloride 84, and potassium 3.9 mEq. per liter; total protein was 5.5 gm. per 100 ml., nonprotein nitrogen 15 mg. and sugar 205 mg. per 100 ml.

Three hours later after a profuse urine output the sodium was 118, chloride 85, and potassium 4.3 mEq. per liter. The serum water-solute ratio was 4.04 ml. per milliosmol.

The urine was dilute, ranging between 1.001 and 1.010 during the next 12 hours. In light of this no intravenous hypertonic solution was given. The patient voided 16 times during the first day and an equal number of times during the second day.

It was estimated that 75 to 100 ml. of urine were passed on each occasion for a total daily output of 1500 ml. on each of the first 2 hospital days. Throughout this time she refused oral fluid.

During the 12 hours following admission she became gradually more responsive, and there was no recurrence of seizures. At the end of this period the serum sodium had risen to 132 mEq. per liter and the total protein to 6.9 gm. per 100 ml. There was subsequently complete recovery, and an electroencephalogram taken a few months later was normal.

Comment. Water intoxication is a well known complication of tap water enemas. The risk is increased if for any reason the water cannot be expelled or if there is a large, distended bowel as in megacolon.[19] Rough calculations indicate that the water load in the present instance was in excess of 4000 ml. per square meter per day. Fortunately, the illness and its treatment with barbiturate drugs did not prevent a water diuresis. Hence the severe derangement in water and electrolyte balance was rapidly overcome by the body's homeostatic mechanisms without necessitating the infusion of hypertonic solutions. The prompt diuretic response here is in sharp contrast to the prolonged oliguria of the cases previously cited in which anesthetic agents and opiates played so large a role. In most situations in which the total electrolyte content of the body is normal or nearly so and the kidneys can respond to the excess water by forming large amounts of dilute urine, this method of management is probably preferable. However, when the diagnosis is apparent and the water intoxication sufficiently severe as to cause acute neurologic symptoms, there should be no hesitation in administering hypertonic fluid intravenously.

It is obviously impossible to relate all the neurologic symptoms and signs to any one event in the present case. Certainly the initial convulsions antedated water intoxication, but there can be little doubt that the late seizures and coma were the product of overhydration.

Therapy of "febrile seizures" with enemas is not only potentially dangerous, but also of no established merit. Whenever the physician is confronted by a patient in whom this age-old treatment has been given, water intoxication should be considered.

CASE VI. A 17-year-old boy was referred to the hospital because of temper tantrums and behavior such that he had been required to leave school 2 years previously. During the 2 months prior to entry he had lost 35 pounds in weight. School records showed that he had ceased to grow at age 13, though until that time stature had been normal. Cessation of linear growth was not referable to epiphysial closure, since pubic, axillary and facial hair never developed; the genitals were infantile and the voice high-pitched. A diagnosis of panhypopituitarism was made. He was treated with thyroid. Vomiting and polyuria were ascribed to his behavioral disturbance and psychiatric follow-up advised.

Four months later he was readmitted to the hospital with extreme dehydration. In the interval since his first admission he had become far easier to manage. However, he was sleeping 12 to 14 hours at night and taking 2- to 4-hour daytime naps from which he was difficult to arouse. On admission the serum water-solute ratio was 3.4 ml.

per milliosmol (sodium 147, chloride 111 mEq. per liter), while urine showed paradoxical dilution with a water-solute ratio of 4.75 ml. per milliosmol (specific gravity, 1.004). These values established the diagnosis of diabetes insipidus. There was bilateral pallor of the optic disks, and there were defects in the upper temporal quadrants of both visual fields. Lumbar puncture yielded fluid under a pressure of 80 mm. of water. The cell count was 4 lymphocytes per cubic millimeter and protein concentration 108 mg. per 100 ml.

During a week's stay in the hospital the patient became progressively more somnolent. Despite dehydration, he seemed to experience little sensation of thirst and vomited the food and fluids urged upon him. In an attempt to improve nutrition and hydration a nasogastric tube was inserted.

Figure 35 illustrates the difficulty encountered when the physician attempts to substitute for the normal operation of one of his patient's homeostatic regulatory

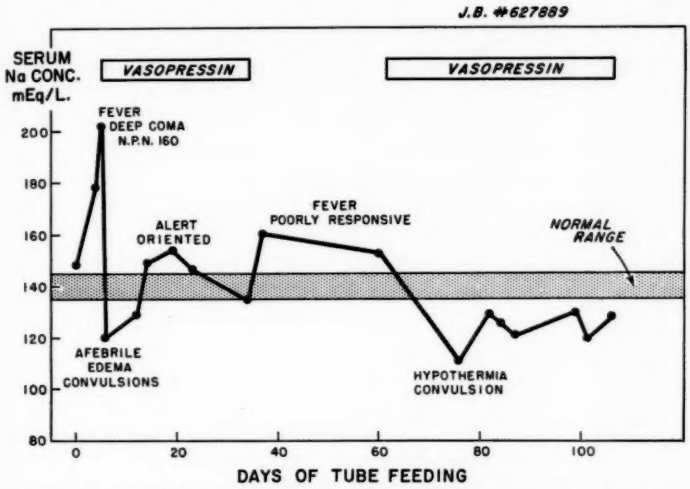

Fig. 35. Serum sodium concentration values during a prolonged period of nasogastric tube feeding of a patient with diabetes insipidus and panhypopituitarism secondary to inoperable brain tumor (case VI).

systems. During the first few days of tube feeding the boy lapsed into deep coma with fever which was attributed to progression of his central nervous system disease. But the laboratory data showed that extreme hypernatremia and azotemia had developed. Overzealous treatment with dilution of the tube feeding mixture and depot vasopressin resulted then in hyponatremia (serum sodium 120 mEq. per liter), the development of peripheral edema and the convulsions of water intoxication. Further modification of the tube feeding mixture returned hydration and serum sodium concentration to near normal values, where they were successfully maintained for the next 2 weeks. During this period the patient's state of awareness was so improved that in retrospect it was evident that abnormalities of hydration rather than rapid progression of the central nervous system lesion had been responsible for the earlier neurologic deterioration.

Between the nineteenth and thirty-fourth days of tube feeding a slow, steady decline in serum sodium concentration was observed. This led to the unfortunate decision to omit vasopressin. Maintenance of normal hydration was attempted by further diluting the tube feeding mixture and by allowing the patient to take water according to thirst. As is depicted in the figure, this was not entirely successful. Again, the patient was not thirsty in spite of evident dehydration. Once more fever, somnolence and con-

fusion in association with high serum sodium values developed. Vasopressin was reinstituted on the sixty-first day, but was unaccompanied by curtailment of fluid intake adequate to compensate for the reduction in urinary water loss. Water intoxication with convulsions and hypothermia resulted. Some improvement in water balance followed the acute episode of the seventy-fifth day. The patient was discharged ultimately to an institution for terminal care, his hypothalamic tumor having proved inoperable.

Comment. This case exemplifies the difficulty encountered when the stuporous neurologic patient must be maintained on parenteral or nasogastric fluids. Even in the absence of diabetes insipidus or other defects of the endocrine regulatory mechanisms, management may be complex. For instance, many neurosurgical patients undergo postoperatively a protracted period of negative nitrogen balance with urinary losses up to 20 gm. per square meter per day. The nitrogen is excreted chiefly as urea, and this is equivalent to an osmolar load of 700 milliosmols. If insufficient water is given to provide for the resultant osmotic diuresis, dehydration with hyperelectrolytemia will occur. The water requirement for urine formation will vary according to the following considerations. If the total osmolar load is relatively small (400 to 600 milliosmols per square meter for 24 hours), kidney function normal and no diabetes insipidus present, a water allowance of 1 ml. per milliosmol of urinary solute is sufficient. If the solute load is much larger (1200 to 1500 milliosmols per square meter per 24 hours), as may be the case in the catabolic situation just mentioned or when there is glycosuria, a water allowance of 2 ml. per milliosmol may be required. In diabetes insipidus, when vasopressin is not used, water allowances for total solute output values comparable with those cited above should approximate 15 and 10 ml. per milliosmol, respectively. The nephritic patient who is unable to concentrate urine, in other words, one whose urine has a fixed specific gravity, will need a water allowance for urine formation of approximately 3 ml. per milliosmol of total urinary solute. In all circumstances additional water must be given to cover insensible losses.

Comatose patients suffer more commonly from water intoxication than from hypertonic dehydration. This occurred twice during the course of this boy's treatment. This may be the result simply of excessive intake overtaxing normally functioning excretory mechanisms, or it may result from a temporary reduction of excretory capacity. The inhalation anesthetics, especially ether and cyclopropane, and morphine have an influence of this latter type which has already been illustrated. These agents share in common a primary renal, nonhormonal, antidiuretic action. In addition, ether[1] and, in certain circumstances, morphine[6] stimulate antidiuretic hormone release by the intact neurohypophysis. Brain injury, whether traumatic, due to meningitis, or the result of neurosurgery, particularly in the area of the hypothalamus, may

also result in sharp curtailment of urine flow. This antidiuresis has all the characteristics of a vasopressin response, but cannot be overcome by elevation of the water-solute ratio of body fluids or by hypervolemia. It appears to be due to loss of integrity of the blood-brain barrier and pathologic "leakage" of vasopressin from the hypothalamus, where normally the hormone is stored, secretion occurring only in response to need.

When hormonal "leakage" of this type occurs and water balance becomes strongly positive as a result of fluid therapy, a second reaction takes place, that of excessive urinary sodium loss.[13, 14] Our experience suggests that such "sodium dumping" is identical with so-called cerebral salt wasting,[18] since it can be demonstrated in the absence of any central nervous system disease by simple water loading of the normal person. In the presence of vasopressin the large renal sodium output which characterizes this second reaction aggravates the tendency to water intoxication, for rapid loss of sodium and accompanying anion in hypertonic urine will cause an increase in the water-solute ratio of body fluids. For instance, when 1 milliosmol of solute which in the body was accompanied by 3.5 ml. of water, is excreted in only 1 ml. of urine, there is a net gain in body water of 2.5 ml. When this involves several hundred milliosmols, the effect on the water-solute ratio of body fluids will be considerable.

The patient whose sensation of thirst cannot be relied upon to govern intake provides a challenging situation for the physician in charge. Nevertheless extensive laboratory facilities are not necessary for proper management. A careful graphic record of intake and output, frequent body weights and determinations of the water-solute ratio and nonprotein nitrogen in serum and urine will ordinarily suffice.

Case VII. A 14½-year-old, ninth grade schoolboy was first seen for the complaints of short stature and polyuria. He was a normally proportioned, sexually immature boy of average height for 7½ and of normal weight for 9 years. Neurologic examination was normal save for bilateral pallor of the optic disks. Visual fields were full. Radiographs of the skull showed the sella turcica to be enlarged with deepening of the floor and upward tilting of the posterior clinoids. Lumbar puncture yielded clear fluid under an initial pressure of 200 mm. of water. The cerebrospinal fluid protein was 31 and sugar 79 mg. per 100 ml. Daily urine volume averaged 5 liters. Water deprivation over a 12-hour period resulted in a fall in the water-solute ratio of serum from a normal value of 3.57 to 3.11 ml. per milliosmol. Simultaneously, the urine water-solute ratio fell from 9.8 ml. per milliosmol (specific gravity 1.003) to 2.2 ml. per milliosmol (specific gravity 1.014). Urinary 17-ketosteroids were 1.0 mg. per 24 hours; F.S.H. was negative at 3.3 mouse units, and serum protein-bound iodine was 2.8 gammas per 100 ml. These findings led to a preoperative diagnosis of panhypopituitarism with mild diabetes insipidus due to an intrasellar tumor with suprasellar extension.

Prior to left frontal craniotomy the patient was transferred to the Metabolic Unit in order that detailed studies of water and electrolyte balance could be carried out during the period of surgery and immediately postoperatively. After preliminary medication with 40 mg. of Demerol and 0.3 mg. of atropine, anesthesia was induced

with ether and maintained over a 4-hour period. As the orbital surface of the left frontal lobe was elevated, a firm, yellow, nodular mass presented between the two optic nerves. It was possible to remove virtually all this tumor, which extended to occupy the entire sella turcica. It proved to be a solid craniopharyngioma. Except as described below, the postoperative course was smooth, and, on substitution therapy, the patient has done well in the ensuing 5 years.

Some of the metabolic events accompanying anesthesia, surgery and the early postoperative hours are shown in Figure 36. The section at the top of the figure depicts the trend of the serum water-solute ratio over a period of 48 hours beginning just before surgery. The rapid rise commencing at the time of anesthesia induction and culminating 20 hours later in association with convulsive seizures is notable. Data

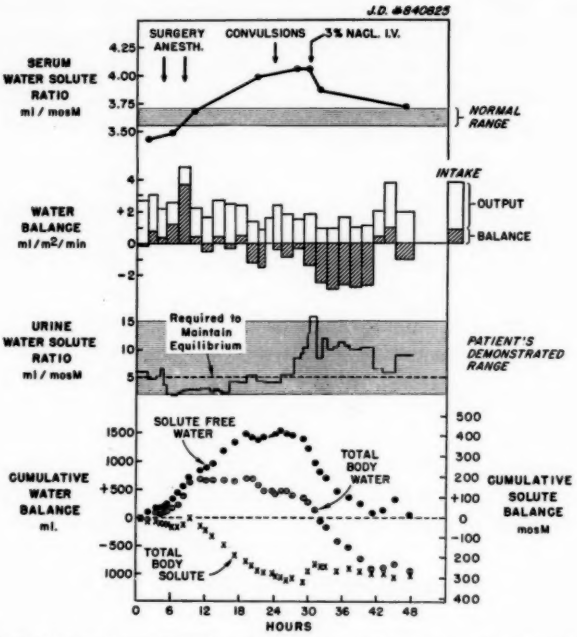

Fig. 36. Operative and postoperative metabolic events in a patient undergoing craniotomy (case VII).

pertinent to the genesis of this episode of water intoxication and its treatment are given in the sections below.

In the second section of the figure, water balance is shown. The height of the columns above the baseline indicates rate of intake of intravenous fluid, which contained dextrose, 2.5 gm. per 100 ml., and, in milliequivalents per liter, sodium 20, potassium 17.5, chloride 20, phosphate 7.5 and lactate 7.5. Rate of output, including the relatively small moiety due to insensible loss, is shown by plotting downward from the top of the intake columns toward the baseline. Within any given column a shaded area lying above the baseline indicates output less than intake and positive balance. A shaded area extending below the baseline indicates output greater than intake and, hence, negative balance. It can be seen that intake, though variable from period to period, averaged about 3 liters per square meter per 24 hours. From a preoperative situation of equilibrium the patient went immediately into positive water

balance with the start of anesthesia, returned to equilibrium at the end of the operation and then had a negative water balance.

In the third section of the figure the water-solute ratio of the urine is shown. The shaded area indicates the range through which preoperative studies had shown the patient capable of varying. From these studies it had been calculated that if fluids of the composition given above and in the amount of 3 liters per square meter per 24 hours were continued through the operative procedure, and if urine with an average water-solute ratio of 5 ml. per milliosmol were excreted, water balance would obtain. Note that with induction of ether anesthesia and as urine flow diminished (see section above) the urine water-solute ratio fell sharply and remained low throughout the operation. Postoperatively there was a rapid rise to high values and ultimate return to the preoperative status.

In the last section of the chart, cumulative water and solute balances are shown. Cumulative balance of total body water is given by the open points. Coincident with anesthesia and surgery, balance became positive. After an accumulation of under 700 ml. no further gains occurred, and later there was a rapid decline across the baseline to an ultimate water deficit of approximately 1 liter. Total body solute balance derived as the difference between the electrolyte intake from parenteral fluids and the total urinary solute output minus urea is shown by the crossed points. For approximately the first 10 hours of observation and over the same period during which the cumulative total body water balance became positive, solute balance showed little net change. Thereafter a rapidly accumulating negative solute balance developed with loss of approximately 300 milliosmols between the tenth and thirtieth hours of observation. This negative trend was interrupted at the thirtieth hour by the administration of 100 milliosmols as hypertonic (3 per cent) saline given intravenously. At the fortieth hour note that the cumulative water and solute balance lines arrive at a common meeting point below the baseline.

The third set of closed points show the cumulative balance of "solute-free" water. This may be defined as the amount of water present in the body in excess of that which would maintain a normal relationship between water and the solutes simultaneously present. During the initial 10 hours when there was little change in total solute balance and rapid water accumulation, the solute-free water rose approximately parallel to total body water balance. In the next 10-hour period when there was little or no change in total body water balance, but a rapid urinary loss of body solute, solute-free water rose further, showing a reciprocal relationship with the solute balance. These correlations provide the explanation for the continued rise in the serum water-solute ratio, water intoxication and convulsions in the absence of any notable excess of total body water (see top section of figure). In the 30 to 40 hours when the negative solute balance was reversed by administration of hypertonic saline and cumulative total body water balance fell from slightly positive to markedly negative values, there resulted a rapid decline in solute-free water and, simultaneously, a return towards normal of the serum water-solute ratio.

Comment. The development of water intoxication in this patient might be surprising if figures were available only for body weight or total body water balance. The maximum positive water balance which developed was 640 ml. in a 28-kg. person, equivalent to an accumulation of 2.4 per cent. Normally such an accumulation is innocuous and quickly eliminated by water diuresis. However, in the present patient and despite clinical diabetes insipidus, normal urine dilution was prevented by the influence of ether anesthesia and surgery in the region of the hypothalamus. A number of patients with fully developed diabetes insipidus, some studied by us, and others recorded in the literature,[9, 12] have manifested a similar antidiuretic response. As shown in the figure by the sharp drop in the urinary water-solute ratio, hypo-

thalamic vasopressin "leakage" contributed substantially to this phenomenon. Whenever an abnormal accumulation of water fails to be rapidly dissipated, the body brings into play, after a latent period of 5 to 10 hours, its second defensive reaction which prevents further water accumulation: namely, the rapid renal elimination of sodium with chloride as the predominant accompanying anion. While this second line of defense tends to prevent further water accumulation, it accelerates development of water intoxication. The mechanism, previously discussed hypothetically, is here shown in action by the course of the points indicating accumulation of solute-free water. In such a circumstance treatment with hypertonic saline is specific. The amount of saline necessary is readily calculated if two principles are kept in mind. First, in a patient with a severe metabolic disorder a little movement in the right direction is usually all that is required to produce rapid clinical improvement. Secondly, in giving hypertonic saline it should be remembered that the osmotic effect is exerted throughout body water despite the fact that the sodium and chloride are largely restricted in distribution to the extracellular compartment.[3, 15] Hence for a patient such as the one illustrated we can calculate normal total body water as 60 per cent of body weight (28 kg.) or 16.8 liters. Normal total body solute is equal to 1 milliosmol for each 3.6 ml. of total body water, or 4670 milliosmols. At the time of this boy's convulsion his serum water-solute ratio was 4.0 ml. per milliosmol, indicating an excess of solute-free water of (4670 milliosmols $\times$ 4.0 ml. $=$ 18.7 L. $-$ 16.8 L. $=$ 1.9 L.) 1.9 liters.* The requisite amount of solute to bring this volume of solute-free water to a normal water-solute ratio would be calculated as 1 milliosmol for each 3.6 milliliters, or 528 milliosmols. Remembering the first principle above, the calculated full requirement may be reduced at least 50 per cent for initial trial. Thus, in this circumstance, 250 milliosmols which would be delivered by 250 ml. of 3 per cent saline would constitute an appropriate dose. Actually the boy was given only 100 ml. of 3 per cent saline with the dramatic effects illustrated.†

CASE VIII. A 6-week-old girl was admitted because of diarrhea and dehydration of 2 days' duration. The temperature was 97.8° F., respirations 32 and pulse 168 per minute. She appeared desperately ill, was marasmic, limp and cyanotic. The fontanel was deeply sunken, and the sutures were overriding. A watery stool was cultured, but no pathogenic organisms recovered.

* The slight discrepancy between the excess solute-free water of Figure 36 and the present calculation depends upon the fact that the boy's difficulty was in part due to solute deficiency, in part, excess water.

† In the absence of means for direct measurement of serum osmolality, a close approximation can be obtained by multiplication of serum sodium concentration by 2 and addition of 10. As noted earlier, the water-solute ratio is simply the reciprocal of osmolality.

The serum sodium was 160 and potassium 7.5 mEq. per liter; the total protein 7.3, and hemoglobin 15.0 gm. per 100 ml. A diagnosis of hypertonic dehydration was made, and over the next 20 hours 35 ml. of 0.58 per cent (two thirds normal) saline in 5 per cent dextrose, 25 ml. of plasma and 410 ml. of a multiple electrolyte solution* in 5 per cent dextrose and water were given intravenously (2900 ml. per square meter per day). After this, irregular myoclonic twitchings and generalized convulsions occurred which were controlled by 30 mg. of Sodium Amytal intravenously. During the seizure period serum sodium was 147 and potassium 6.7 mEq. per liter; the serum water was 3.4 ml. per milliosmol, calcium 9.6 mg. and phosphorus 6.8 mg. per 100 ml. These findings suggested the possibility of so-called intracellular water intoxication frequently encountered in the course of treatment of hypernatremia.[8, 21, 26] Actually, however, treatment had been relatively conservative with regard to the rapidity of reduction of the serum water-solute ratio, and in view of this it seemed appropriate to raise the question: Was there some other cause for the seizures? It was recalled from the history that the patient had been developing and thriving poorly and that seizures had occurred spontaneously at 2 weeks of age. After recovery from the dehydration and electrolyte imbalance severe developmental retardation was demonstrated. Remarkable transillumination of the frontal regions of the head led to a ventriculogram in which frontal lobe atrophy and agenesis of the corpus callosum were demonstrated.

Comment. This case is included to illustrate the necessity for caution in attributing a given clinical syndrome to any single biochemical or anatomic factor. Here the occurrence of seizures during treatment of hypernatremia with hypotonic fluids was, at first glance, explained exclusively on the basis of so-called intracellular water intoxication.[21] However, the history of previous seizures and demonstration of anatomic defects in the brain demanded reservations in interpretation. It may well be that the electrolyte disturbance was only partially responsible for or even unrelated to the seizures.

The abnormal degree of transillumination deserves special mention. Its persistence unchanged for over a year following the acute episode suggests, as does the ventriculogram, that an anatomic defect of the frontal lobes exists. However, transillumination may be demonstrated in patients with acute hypernatremia, a consequence of shrinkage of the brain and an increase in the space between it and the inner surface of the dura and skull. This sign may disappear with rehydration or persist if a subdural effusion develops.[5]

DISCUSSION

Seldom is a medical report comprised exclusively of a recitation of sins committed in the management of sick patients. It is to be hoped that the cases recorded here will help others to avoid similar mistakes in management of fluid therapy.

SUMMARY

The case histories of eight patients, the majority of whom had primary neurologic disease, have been reviewed to illustrate common errors in

* Sodium 40; potassium 35; chloride 40; phosphate 15; and lactate 20 mEq. per liter.

management of fluid therapy which may result in serious disturbances of water metabolism. The underlying pathophysiology, the clinical manifestations and the treatment of these disturbances are discussed. It has been emphasized that water homeostasis not only is the product of facultative control of renal water excretion, but also depends upon mechanisms which govern intake. In each of the patients discussed the capacity of the homeostatic system concerned with regulation of body water was overtaxed so that it could not fulfill its usual protective role. Mechanisms which govern intake can no longer afford protection when fluids are administered parenterally or by other abnormal routes. The capacity of the kidney to excrete water may be temporarily but seriously reduced by a number of common clinical events. Of particular importance among these are brain injury whether traumatic, infectious or neurosurgical, shock due to hypoproteinemia or blood loss, and the administration of certain pharmacologic agents, especially morphine and the inhalation anesthetics.

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Massachusetts General Hospital
Boston 14, Massachusetts

SALICYLATE INTOXICATION IN INFANTS AND CHILDREN

ROBERT W. WINTERS, M.D.

The problem of salicylate intoxication in infants and children has assumed considerable importance because of the increasingly widespread use of aspirin. In general, cases of salicylism arise out of two situations: (*a*) those in which salicylate, either aspirin or methyl salicylate (oil of wintergreen), has been ingested accidentally, and (*b*) those in which an overdosage of aspirin has been given unwittingly, either by a parent or by a physician, in the treatment of some febrile illness.

Salicylate in large amounts produces several distinct disturbances in metabolism which are reflected by the development of complex and sometimes confusing disorders of acid-base equilibrium. In this paper an attempt is made to reconstruct the pathogenesis of each of these abnormalities of acid-base equilibrium in terms of the basic effects of salicylate. It is only through such an approach that rational therapy can be formulated.

BASIC EFFECTS OF TOXIC AMOUNTS OF SALICYLATE

There are three basic effects of salicylate which directly influence acid-base equilibrium: (*a*) primary increase in pulmonary ventilation, (*b*) increase in metabolic rate and hence in the production of carbon dioxide, and (*c*) disturbances in the metabolism of carbohydrates and lipids resulting in accelerated production of organic acids. Each of these actions and their impact upon acid-base balance will be considered separately.

From the Departments of Pediatrics and Medicine, University of North Carolina School of Medicine, Chapel Hill.

Increase in Pulmonary Alveolar Ventilation

Salicylate causes an increase in pulmonary alveolar ventilation through a direct action upon the neural centers controlling pulmonary ventilation.[27, 36] As a *pure effect*, this action leads to an increase in alveolar ventilation and a consequent fall in alveolar and arterial pCO_2*—i.e., respiratory alkalosis. Such a disturbance is countered by both physicochemical and physiologic mechanisms. The fall in arterial pCO_2 leads to an initial rise in blood pH; buffering by the nonbicarbonate buffers of the blood tends to limit the alkaline shift in pH through the following reaction:

$$[1]\quad B^+HCO_3^- + HBuf. \longrightarrow B^+ Buf.^- + H_2CO_3 \longrightarrow CO_2\uparrow + H_2O$$

where *Buf.* is the nonbicarbonate buffers (principally hemoglobin and oxyhemoglobin). The quantitative characteristics of this type of buffering are shown as line A in Figure 37 (the normal carbon dioxide absorption curve). This line represents the initial displacement pathway of patients with acute respiratory alkalosis.

The principal physiologic adjustment to respiratory alkalosis is a renal one whereby the urine initially becomes alkaline and contains large amounts of bicarbonate, sodium and potassium; chloride excretion, on the other hand, is diminished.[35] The net result of these effects is to increase the plasma chloride and to reduce the plasma bicarbonate. Hence blood pH is reduced toward normal. These effects of the renal adjustment are depicted as lines *a* in Figure 37. Renal compensation is relatively slow in contrast to the nearly instantaneous buffering action of the blood.

Appreciable amounts of sodium and potassium may be lost through this initial renal adjustment to respiratory alkalosis. This, coupled with extrarenal losses of these ions (through vomiting, sweating, and so forth), can lead to depletion of both these cations. In the presence of sodium[23, 35] or potassium[4] depletion, excretion of these ions and of bicarbonate is reduced. The urine becomes acid ("paradoxical aciduria").

* The terms "pCO_2" and "total carbon dioxide content" must be clearly distinguished from each other. The partial pressure of carbon dioxide in alveolar air is termed the *alveolar* pCO_2. When arterial blood equilibrates with alveolar air, a certain amount of carbon dioxide, depending upon the alveolar pCO_2, dissolves in blood, a small fraction of which is hydrated to form carbonic acid. The *arterial* pCO_2 is the partial pressure of carbon dioxide which is necessary to achieve the observed concentration of dissolved carbon dioxide in blood; ordinarily the alveolar and arterial pCO_2 values are the same. The alveolar pCO_2 directly determines the concentration of carbonic acid in blood, the denominator of the Henderson-Hasselbalch equation, since H_2CO_3 (millimols per liter) equals constant times alveolar pCO_2 (millimeters of mercury). The total carbon dioxide content of the plasma, on the other hand, represents the sum of dissolved carbon dioxide, carbonic acid and bicarbonate.

There is another type of physiologic mechanism tending to restore pH toward normal. Various studies[11, 14] have demonstrated that in acute respiratory alkalosis, hydrogen ions enter the extracellular fluid from the cells and/or bone in exchange for extracellular cation. In addition, organic acids, principally lactic acid, move from the cells into the extracellular fluid, and the organic anion concentration of the serum rises.[14]

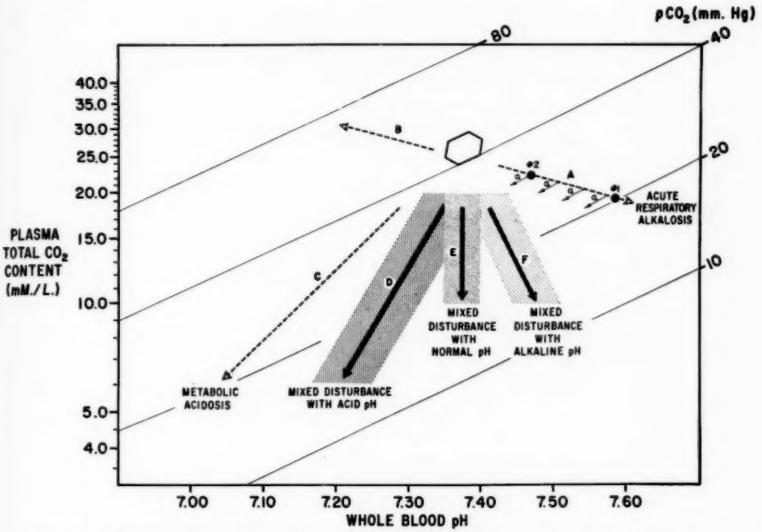

Fig. 37. Effects of the basic actions of salicylate upon acid-base equilibrium and the typical displacements encountered in mixed disturbances in salicylism.

Line *A* represents the *pure effect* of an increase in alveolar ventilation; line *B* is the *pure effect* of an increase in CO_2 production; line *C* is the usual pathway of uncomplicated metabolic acidosis.[39] Approximate areas depicting the various mixed disturbances in salicylism are shown by lines *D*, *E*, and *F*.[39] See text for further discussion. The basic grid is a graphic representation of the Henderson-Hasselbalch equation, in which the logarithm of the plasma total CO_2 content is plotted on the ordinate and whole blood pH is plotted on the abscissa. Any given set of values for these 2 variables fixes the value for pCO_2, isopleths for which are shown as the diagonal lines. The hexagonal area in the center is the approximately normal range.

Besides producing a primary increase in alveolar ventilation, salicylate also increases the sensitivity of the respiratory center to the physiologic respiratory stimuli of pCO_2 and hydrogen ion concentration.[1, 36] Hence an increment in the concentration in the blood of either of these physiologic stimuli produces a greater than normal increment in alveolar ventilation. The implications of this action of salicylate will be discussed more in detail below.

Increase in Metabolic Rate

Large amounts of salicylate cause increases in metabolic rate with attendant increases in oxygen consumption, carbon dioxide production and heat production.[9, 36] It is this last effect which is principally responsible for the elevated body temperature in salicylate poisoning.

The mechanism of this increase in metabolic rate produced by salicylate is related to the action of the drug in uncoupling oxidative phosphorylation.[7]

The *pure effect* of an increase in carbon dioxide production upon acid-base equilibrium is to produce a rise in pCO_2—i.e., respiratory acidosis. This pathway is depicted as line *B* in Figure 37. Actually, in nearly all cases of salicylism, pulmonary alveolar ventilation increases to a greater extent than does the increase in carbon dioxide production, so that the pCO_2 falls.

In a steady state the interrelationships between alveolar ventilation (V_A), carbon dioxide production and alveolar (or arterial) pCO_2 are described by the following expression:

$$[2] \quad V_A \propto \frac{CO_2 \text{ production}}{pCO_2}$$

If carbon dioxide production remains the same, a twofold increase in alveolar ventilation will be accompanied by a fall in pCO_2 to half its control value. This is represented by point 1 on line *A* in Figure 37. On the other hand, a twofold increase in alveolar ventilation with a 50 per cent increase in the production of carbon dioxide would cause pCO_2 to fall only half as far (*cf.* point 2, line A, Fig. 37). In most cases of salicylism alveolar ventilation is increased; carbon dioxide production is also increased, but to a less extent, so that pCO_2 falls, but to a less degree than if no increase in carbon dioxide production had occurred.

Disturbances in Carbohydrate and Lipid Metabolism

Several abnormalities in the metabolism of carbohydrate and lipid have been described following the administration of salicylate. Glycogenolysis is speeded,[21] while the synthesis of glycogen by the liver is inhibited.[37] These actions may be related to the stimulation of metabolic rate and to the defective production of high-energy phosphate bonds due to uncoupling of oxidative phosphorylation. Evidently the liver is still producing glucose at a rate faster than its utilization by the peripheral tissues, since the blood sugar is usually somewhat elevated in experimental and clinical salicylate poisoning.[16, 34]

Related to these defects, or perhaps to a more specific enzymatic defect in the Krebs tricarboxylic acid cycle,[19, 24] is the acceleration of fatty acid catabolism and the production of ketone bodies by the liver. Ketosis in salicylism is conditioned by age, being common in the infant and young child, but uncommon in the older child and adult except in extremely severe cases.

The *pure effect* of any increase in plasma ketone acids upon acid-base equilibrium is to produce a metabolic acidosis. This is countered by both physicochemical and physiologic mechanisms.

Blood buffering occurs by both bicarbonate and nonbicarbonate buffer systems:

$$[3]\quad H^+A^- + B^+HCO_3^- \longrightarrow B^+A^- + H_2CO_3$$

$$[4]\quad H^+A^- + B^+\,Buf. \longrightarrow B^+A^- + HBuf.$$

where *HA* is a strong acid such as a ketone acid. As a result of these reactions, pH shift toward the acid side is limited.

Physiologic adjustments, both renal and respiratory, further diminish the acidosis. Respiration is stimulated immediately by the rise in pCO_2 due to buffering (equation 3), as well as by the low blood pH. In well established metabolic acidosis low blood pH alone is the stimulus for hyperventilation, and pCO_2 is below normal.[15] The average acid-base displacement pathway of uncomplicated metabolic acidosis is depicted as line *C* in Figure 37.

The renal adjustment to metabolic acidosis initially is characterized by increased rates of excretion of sodium, potassium, titratable acid, and the anion of the loading acid, as well as by an avid reabsorption of bicarbonate; later, with full augmentation of ammonia production, ammonium excretion rises while the excretion of other cations is reduced.[30]

DISTURBANCES OF ACID-BASE EQUILIBRIUM IN SALICYLISM

Several types of disturbances of acid-base equilibrium have been observed in clinical salicylate intoxication. Of these the most important and most common, at least in the infant and young child, is a mixed disturbance characterized by *primary* disturbances both in the respiratory and in the metabolic components of acid-base equilibrium.[33, 39] In older children and adults respiratory alkalosis unaccompanied by any discernible *primary* metabolic disturbance is the typical abnormality.[39]

Mixed Disturbances

Mixed disturbances of acid-base equilibrium in salicylism consist of *primary* disturbances in the respiratory component (tending to produce respiratory alkalosis) and in the metabolic component (tending to produce metabolic acidosis). All patients with mixed disturbances of this type present with low values for total carbon dioxide content and for pCO_2. Blood pH, on the other hand, may be acid, normal or alkaline.

The varying blood pH in the mixed disturbances has been interpreted

as reflecting the fortuitous relationship between the intensity of the *primary* respiratory disturbances on the one hand (reflected by pCO_2) and the intensity of the *primary* metabolic disturbances on the other (reflected by plasma bicarbonate).[39] This concept differs from the often-cited sequence of respiratory alkalosis followed by metabolic acidosis in salicylism by emphasizing the simultaneity of the two independent disturbances.

The mixed disturbance with acid pH differs conceptually from uncomplicated metabolic acidosis, such as that occurring in diarrhea, by

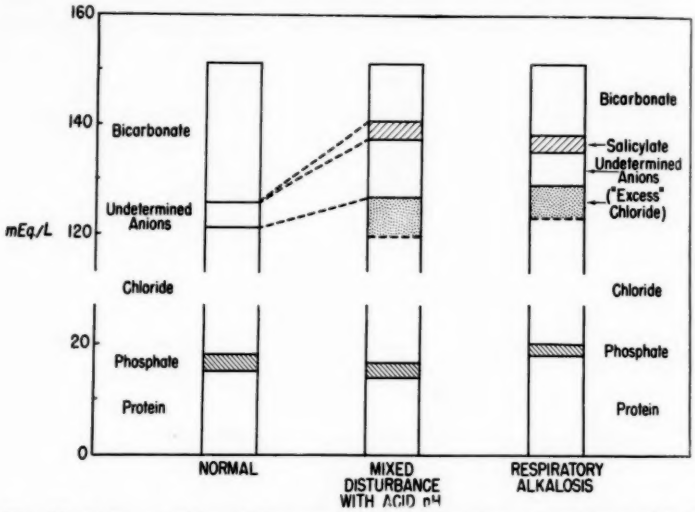

Fig. 38. Anion partition of the serum in normal patients, in patients with the mixed disturbance and acid pH and in partially compensated respiratory alkalosis. (Data from published and unpublished studies by the author.[38, 39])

the fact that in the former there is an additional stimulus for hyperventilation over and above that due to the acidosis per se. These two states are compared in Figure 37 (lines *C* and *D*). At any given total carbon dioxide content, patients with salicylism and acidosis have higher values for blood pH and hence lower values for pCO_2 than do patients with metabolic acidosis due to other causes.

In contrast to the manifestations of the mixed disturbance in the typical acidotic patient, a few patients presenting with acid values for blood pH do not have evidence of *independent* respiratory stimulation. Such patients show unexpected low values for blood pH and relatively high values for pCO_2 compared to those seen in the mixed disturbance. Study of four of such patients by Winters et al.[39] suggested that in all there was some limitation of respiratory activity either because of de-

pressant agents ingested along with salicylate or perhaps because of the unusual severity of the intoxication.

The anion composition of the serum of patients with a mixed disturbance and an acid pH is diagrammed in Figure 38, where it is compared to the normal. The accumulation of undetermined anions, probably largely ketone bodies, is the chief abnormality, though some degree of hyperchloremia ("excess chloride") is also present. Salicylic acid contributes only slightly to the acidosis.

The mixed disturbances with normal or alkaline values for blood pH are shown as lines *E* and *F* in Figure 37. In these disorders the metabolic component resembles that of the preceding disturbance (see Fig. 38), but is less severe, although still discernible. It is noteworthy that in all three of the mixed disturbances, deviations of blood pH are not extreme, although considerable reductions of total carbon dioxide content and of pCO_2 may be present.

Respiratory Alkalosis

Respiratory alkalosis unaccompanied by any discernible *primary* metabolic component is the typical disturbance of older children and adults with salicylism. As indicated above, the initial pathway of this disorder is defined by the normal carbon dioxide absorption curve (line *A*, Fig. 37). The effects of the renal and extrarenal compensatory mechanisms are to produce deviations in the direction of the lines marked *a* in Figure 37. The extent to which any patient moves towards a normal pH is dependent upon the duration of the disturbance and the integrity of the compensatory mechanisms, principally those of the kidney. Since complete return to normal pH probably requires a matter of some days, patients with a respiratory alkalosis due to salicylism of short duration fall somewhere between line *A* and line *F*. A normal or nearly normal pH may occur if the disturbance is of longer duration.

The anion partition of patients with partially compensated respiratory alkalosis is depicted in Figure 38. The similarities to the mixed disturbance are striking, although the mechanisms responsible for the various alterations in anions are quite different. In respiratory alkalosis the decrease in bicarbonate, the increase in undetermined anion (largely lactate) and the increase in chloride are all secondary to blood buffering or to renal and extrarenal *compensatory* adjustments rather than the result of *primary* disturbances, as is the case with the mixed disturbance and acid pH.

PATHWAYS OF RECOVERY

The pathways of recovery from the various disturbances of acid-base equilibrium in salicylate poisoning are of considerable importance, since

they are conditioned by the design of the particular therapy administered.

Mixed Disturbance with Acid pH

In this group of patients the characteristic feature of recovery is the failure of pCO_2 to rise as fast as the rise in total carbon dioxide content, indicating a persistence of hyperventilation. Patients initially presenting with an acidosis and treated with adequate amounts of sodium, chloride, potassium, water and carbohydrate, but little or no sodium bicarbonate

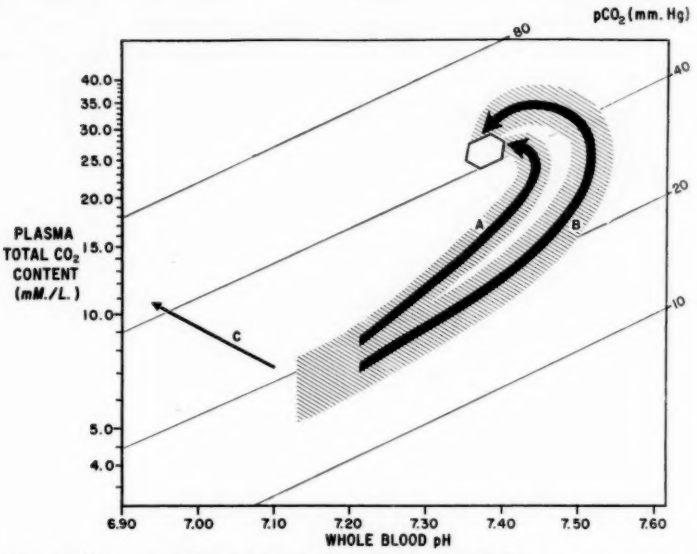

Fig. 39. Recovery pathways from initial acidosis of salicylism.
Curve *A* represents pathway of patients treated with little or no alkalinizing salts; curve *B* represents pathway of patients treated with large amounts of alkalinizing salts; line *C* represents initial course of 2 patients who had superimposed acute respiratory depression. All pathways represent smoothed curves to published data.[12, 39]

(or sodium lactate), tend to recover through a pathway involving a significant tendency toward the development of alkalosis associated with a low pCO_2 (pathway *A*, Fig. 39). This tendency toward alkalosis can be both accelerated and exaggerated when large amounts of alkalinizing salts are given, as shown in pathway *B*, Figure 39. Undoubtedly the development of potassium depletion would also favor the development of alkalosis during recovery.

The fact that pCO_2 remains lower than normal during the acute phases of recovery in salicylism has several practical implications. It is

apparent that if the total carbon dioxide content is to be followed as a sole measure of the disturbance of the acid-base equilibrium, the achievement of values between 15 and 20 millimols per liter within the first 24 to 36 hours will be most likely associated with normal values for blood pH, whereas normal or supernormal values for total carbon dioxide content during this time will generally be associated with definite, perhaps serious, degrees of alkalosis.

Mixed Disturbance with Normal pH

Such limited data as are available[38] concerning the recovery from this type of disturbance suggest that at least three possible pathways occur: (*a*) a transition to a mixed disturbance with an acid pH due to the development of a more severe ketosis, (*b*) a transition to a mixed disturbance with alkaline pH because of decreasing severity of ketosis, and (*c*) recovery by pathway with no significant deviation of pH from normal. Patients with this type of initial disturbance are generally less seriously ill than those presenting with acidosis. Perhaps for this reason the deviations observed during recovery are less marked.

Groups with Alkaline pH

Most alkalotic patients recover through a pathway depicted as line *A* in Figure 40 merely by the withdrawal of salicylate. It is commonly stated that respiratory alkalosis is the initial event in salicylism and, at least in some cases, is followed by the development of metabolic acidosis. This sequence has rarely been documented; the possibility that the initial alkalosis is only of short duration and therefore remains largely undetected, of course, cannot be excluded. The author has studied only 1 patient in whom this sequence definitely occurred, and this was attributed to an error in the management whereby the child received no exogenous carbohydrate for 36 hours. Although initially alkalotic, the child had a severe ketosis at the end of this period. This type of pathway is shown as line *C* in Figure 40. Theoretically, lesser degrees of ketosis superimposed upon an initial alkalosis could lead to a mixed disturbance with a normal pH rather than an acid pH; this type of pathway is depicted as line *B* in Figure 40.

Finally, an additional pathway (line *D* in Fig. 40) depicts the situation if large amounts of sodium bicarbonate or sodium lactate were to be given to an initially alkalotic patient who had been mistakenly diagnosed as having metabolic acidosis on the basis of a low total carbon dioxide content alone. In such a situation an extreme degree of alkalosis may be produced, since pCO_2 would remain low, owing to stimulation of the respiratory center by salicylate, whereas the serum

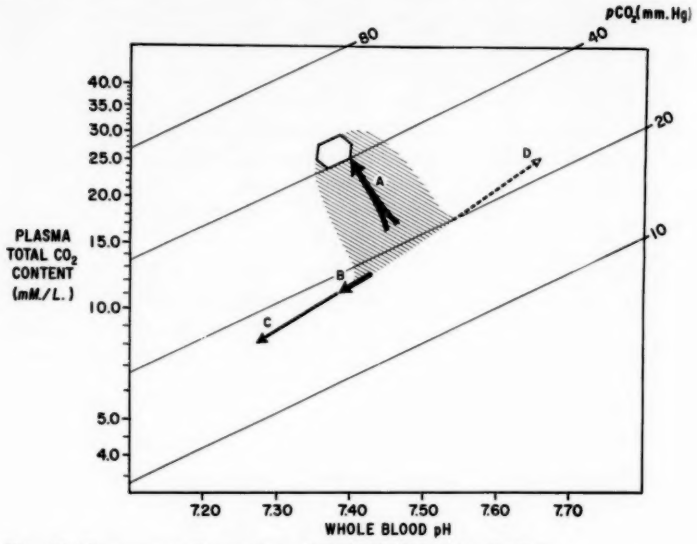

Fig. 40. Recovery pathways from initial alkalosis of salicylism.
Curve *A* represents usual pathway; curves *B* and *C* show transition to mixed disturbances with normal and acid pH, respectively. Curve *D* is expected pathway were an initially alkalotic patient given alkalinizing salts. Curve *A* idealized from unpublished studies; [28, 38] curves *B*, *C* and *D* are largely hypothetical.

bicarbonate would rise because of the administration of sodium bicarbonate or sodium lactate. Such a pathway may be accompanied by severe tetanic symptoms, generalized convulsions and even death.

SIGNS AND SYMPTOMS

Hyperpnea is the outstanding sign of salicylate poisoning. It is one of the most valuable clues in deciding in any instance whether the child has received enough salicylate to constitute a serious threat. Tinnitus, vomiting, sweating, flushing of the skin and fever all may be present, but, being either subjective or relatively nonspecific, do not contribute to the diagnosis in the infant and young child. In cases due to accidental ingestion there may be a lag of several hours between the ingestion of salicylate and the appearance of any of these symptoms and signs. In cases due to overdosage the signs and symptoms develop gradually and may be misinterpreted as being due to the condition being treated.

Moderate dehydration is usually present in the seriously poisoned child. Polyuria is often present, at least initially, although in some severely poisoned patients oliguria and acute tubular necrosis occur.[8]

Bleeding from the nose, gastrointestinal tract or into the skin may occur, and intracranial hemorrhage is a cause of death.

In alkalotic patients the Chvostek and Trousseau signs may be positive. Failure to elicit these signs, however, does not exclude alkalosis.

Disorientation, acute pulmonary edema, convulsions and coma may occur in severely intoxicated patients.

LABORATORY FINDINGS

The hemogram often reveals some increase in packed cell volume apparently due to dehydration. A leukocytosis of up to 20,000 cells per cubic millimeter may occur, even in cases due to accidental ingestion in which the role of preceding infection can be excluded. Urinalysis may show a concentrated urine, but more often the urine is dilute, reflecting the increase in urine flow due to an increased solute excretion and possible potassium depletion. Slight proteinuria and some formed elements are usually present in the urine. Reducing substance detected by Benedict's test is nearly always present in a small amount. This is due principally to the metabolic end products of salicylate, but in some instances glucose may also be present. The presence of the latter should be sought, using specific glucose oxidase tests. Ketonuria, detected by the nitroprusside test, is often marked, especially in infants and young children. Unlike the ferric chloride test, the nitroprusside test does not give falsely positive results in the presence of salicylate.

Ferric chloride reagent, on the other hand, is sensitive to salicylate and gives a purple color in the presence of the drug. Salicylate may be differentiated from ketones in the ferric chloride test by the fact that ketones can be volatilized by acidification and boiling of the urine; persistence of a positive test is evidence for the presence of salicylate, although other substances, notably coal tar dyes, are also nonvolatile and will react.

Occult blood may be detected in the vomitus or stools of patients with salicylate poisoning. Abnormalities in various blood coagulation systems may be present (prothrombin, proaccelerin, proconvertin, fibrinogen), and study of these coagulation factors should be carried out. In some patients bleeding appears to be on the basis of thrombocytopenia rather than upon any abnormalities in the afore-mentioned factors. Platelet counts and tourniquet tests are therefore advisable.

As to the serum electrolytes, the concentration of sodium is usually close to normal, but may be either high or low, depending upon the relative losses and previous replacement of water and sodium. Serum chloride is nearly always elevated with respect to sodium, as discussed above. With serious degrees of dehydration the serum urea-nitrogen is elevated. In these situations the serum inorganic phosphorus also rises, and frequently this rise seems disproportionately great compared to the degree of elevation of the urea-nitrogen.

Initially the serum potassium is usually low-normal or frankly low in alkalotic patients, but is usually normal or elevated in acidotic patients, particularly in the presence of dehydration and elevation of the urea-nitrogen. Hypokalemia develops rapidly, however, during rehydration unless potassium is administered. The serum calcium is normal. Moderate degrees of hyperglycemia rarely exceeding 200 mg. per 100 ml. may be present. Hypoglycemia occurs in rare instances.[3]

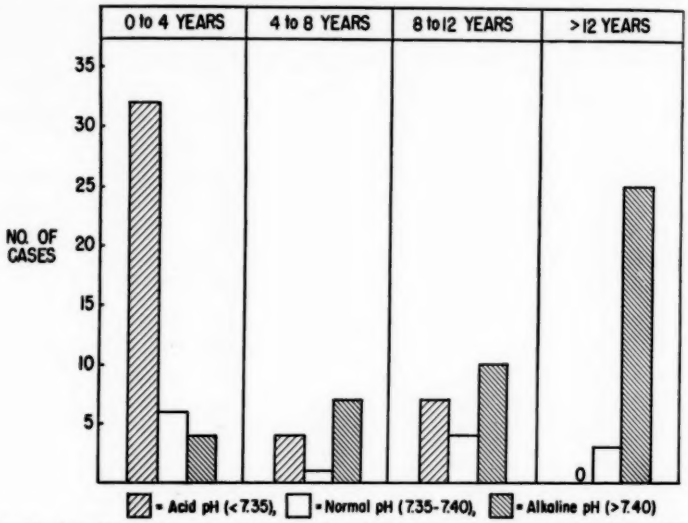

Fig. 41. Age distribution of acid, normal and alkaline pH values in salicylism. (Data for this figure taken from literature.[39])

The determination of the concentration of salicylate in the plasma has its chief value in those cases in which there is no clear history incriminating salicylate. Although it is generally true that salicylate levels exceeding 35 mg. per 100 ml. are associated with clinically important degrees of intoxication, the correlation of the absolute salicylate levels with the clinical severity is poor in infants and children. Furthermore, especially in infants, levels considerably less than 35 mg. may be associated with serious intoxication.

For accurate diagnosis of the type of acid-base disturbance, whole blood pH and plasma total carbon dioxide content are nearly indispensable.* Lacking measurements for whole blood pH, some inference

* With such data pCO_2 may be calculated from the Henderson-Hasselbalch equation, preferably using the physical constants of Severinghaus et al.[32] or from a nomogram.[25] In the presence of high fever it is important to measure or to calculate blood pH and pCO_2 to the actual body temperature, using the appropriate constants.[6, 29, 32]

can be made about the particular type of acid-base disturbance from clinical data. Figure 41 shows the age distribution of acid, normal and alkaline blood pH values in salicylism. The dominant tendency is for acid values to occur in the younger age group and for alkaline values to occur in older children and adults. In addition, the mode of intoxication, whether due to accidental ingestion or to therapeutic overdosage for some febrile illness, as well as the duration of the disturbance, seems to bear some relation to the initial blood pH.[39] Children presenting with salicylism due to therapeutic overdosage in whom the disturbance is present longer than 24 hours uniformly have acid values for blood pH. On the other hand, when the duration of the intoxication is shorter than 24 hours, blood pH, whether the illness is due to accidental ingestion or to therapeutic overdosage, may be acid, normal or alkaline.

The urine pH is not helpful and may be misleading in the interpretation of the systemic acid-base abnormality. Although an alkaline urine almost certainly would indicate a systemic alkalosis, nearly all alkalotic patients present with *paradoxical aciduria*. Urine pH is acid, of course, in patients who have the mixed disturbance with normal or acid pH.

TREATMENT

The design of therapy for any patient with salicylate poisoning must be formulated on the basis of an accurate understanding of the particular metabolic disturbances present.

Suspected Cases

The problem frequently arises as to the proper management of a child who has just been discovered to have ingested an unknown amount of aspirin, but who shows no definite symptoms of intoxication. In such instances measures designed to remove salicylate from the stomach should be instituted immediately. In the study of this latter problem Arnold et al.[2] obtained evidence in the dog suggesting that induction of emesis was more effective than gastric lavage in removing salicylate. If lavage is to be performed, it is important to aspirate before instilling any fluid. A fluid whose composition is similar to extracellular fluid is suitable.*

Because of the lag between ingestion and the appearance of significant symptoms, there is no assurance that in a suspected case salicylism

* A solution of the following composition may be used: sodium, 150 mEq. per liter; chloride, 120 mEq. per liter; bicarbonate, 30 mEq. per liter. One liter of this solution may be mixed as follows: 800 ml. of isotonic saline solution, 33 ml. of concentrated sodium bicarbonate solution (3.75 gm. per 50 cc., Abbott) and 167 ml. of a glucose solution.

will not develop in spite of apparently successful removal of gastric contents. Either the child should be hospitalized for observation or the parents should be instructed to return the child immediately if any of the significant signs and symptoms (see above) appear.

Overt Cases

Some degree of dehydration with accompanying deficits of sodium and potassium is nearly always present in salicylism of any significant duration. Definitive data as to the magnitude of these deficits are not available, although it is probable that in the serious case they approach or exceed those for diabetic acidosis. In most instances of serious intoxication fluid therapy should be carried out by continuous intravenous infusions rather than by relying upon the oral route. No rigid recommendations for therapy can be made because of the variability of the type and severity of the metabolic disorders encountered in patients with salicylism. In the following the major points of therapy are discussed, and some general recommendations are made. Serial studies of the whole blood pH and of the serum electrolytes are most helpful in formulating a specific therapeutic program and assessing its adequacy in any given patient.

The first phase of therapy should be directed toward *expansion of the volume of the extracellular fluid*. Dehydration extreme enough to cause peripheral vascular collapse should be immediately treated with whole blood transfusion. In most instances, however, overt shock is not present, and the contraction of the extracellular fluid, which is usually isotonic or nearly isotonic with respect to sodium, can be effectively treated with an isotonic sodium solution. The anion composition of this initial hydrating infusion should be decided on the basis of the existing disturbances of acid-base equilibrium. In patients presenting with acid or normal values for blood pH, a solution resembling the composition of normal extracellular fluid (see footnote, p. 293) with respect to sodium, chloride and bicarbonate is appropriate, whereas patients with alkalosis should receive all sodium in the form of sodium chloride. The volumes of the initial hydrating infusion vary according to the degree of dehydration present, but are roughly between 20 and 50 ml. per kilogram of body weight. In the presence of hypernatremia or hyponatremia the sodium concentration of the initial infusion should be appropriately adjusted so that it would tend to return the concentration of sodium in serum to normal.

After the initial expansion of extracellular fluid and in the presence of adequate urine flow, *repair of potassium depletion* should be undertaken by the addition of 2 to 3 mEq. of potassium per kilogram of body weight per day. This amount is distributed in subsequent fluids

so that the final concentration does not exceed about 30 mEq. per liter, and the rate of administration is slow enough to prevent hyperkalemia. This amount should be given on subsequent days or until the patient is receiving adequate potassium by mouth.

Adequate amounts of carbohydrate should be provided in all fluids in an attempt to combat ketosis. Generally a final concentration of 5 or 10 per cent glucose in all fluids is advisable, although profuse glycosuria should be avoided. Invert sugar or fructose may be superior, but has not been adequately evaluated in the ketosis of salicylate poisoning. Insulin given with carbohydrate is of no proved value and probably should not be used.

Maintenance fluid and electrolyte requirements must also be included in the parenteral fluid therapy. These are best calculated by the methods outlined by Darrow (see p. 29*ff.*), using the 100 Calorie unit as the base of reference. In salicylism it is most important to take cognizance of the increase in basal metabolic rate, which is about one and one-half times normal. To this must be added increments for activity and for fever. Hyperventilation, polyuria, sweating and vomiting all increase maintenance requirements for water and for electrolytes. Special attention should be given to the maintenance of adequate urine flow, since this measure alone tends to increase the rate of excretion of salicylate.[22]

Acid-Base Disturbances

In typical patients presenting with a *mixed disturbance and an acid pH* there is ordinarily no great need to attempt to treat the acidosis with large amounts of alkalinizing salts, since the risk from the acidosis is less than the risk from overtreatment. Certainly indiscriminate attempts to alkalinize the urine without regard to the prevailing systemic acid-base disturbance are unwarranted (see below).

In severely poisoned patients who present with low blood pH values (i.e., below 7.15), it is advisable to attempt to treat the acidosis by administration of sodium bicarbonate. The amount to be given cannot be calculated from theoretical considerations. The effect desired is to raise the total carbon dioxide content of the serum by about 4 to 8 millimols per liter; acute restoration of normal values for total carbon dioxide content should be avoided. A safe procedure is to administer from 2 to 4 millimols of sodium bicarbonate per kilogram of body weight and to repeat determinations of total carbon dioxide content and blood pH after the infusion. Subsequent doses of sodium bicarbonate may then be decided, depending upon the effect obtained.

In most cases no specific therapy need be undertaken to combat the *respiratory alkalosis*. The initial blood pH values of such patients rarely exceed 7.55.[39] More serious degrees of alkalosis and tetany nearly always

occur as a result of inappropriate treatment involving administration of sodium bicarbonate. The dangers of producing a severe alkalosis by sodium bicarbonate administration in a patient with respiratory alkalosis are obvious from the foregoing discussion and need no amplification. Attempts to depress the excitability of the respiratory center by respiratory depressant drugs are also to be condemned.[27]

Some authors have advised that the tetany of salicylate intoxication be treated with inhalation of 5 per cent carbon dioxide. Since salicylate sensitizes the respiratory center to pCO_2 (see above), this therapy, to be successful, would probably be attended by a considerable increase in the already elevated level of minute ventilation and might lead to a most distressing degree of dyspnea. The same objection applies to rebreathing the expired air. The use of intravenous calcium should be tried. It was said not to be effective in several reported cases;[13, 18] possibly the doses given were too small. Extreme measures such as curarization and control of ventilation by artificial means have been used with success,[13, 18] although this can hardly be recommended as a routine procedure. It would seem that the most rational way of attacking the problem of tetany in salicylate intoxication, provided the inhalation of carbon dioxide and intravenous calcium were unsuccessful, would be to induce a component of metabolic acidosis. This could be done either by expansion of the extracellular fluid through an infusion of sodium chloride ("dilutional acidosis") or perhaps through administration of an inhibitor of carbonic anhydrase (see below). Obviously such therapy must be carefully monitored through serial determination of pH and total carbon dioxide content.

Measures Designed to Rid the Body of Salicylate

The rate of excretion of free salicylate is conditioned by the pH of the urine, in that the excretion of salicylate rises as the urine pH rises.[17, 22] For this reason, alkalinization of the urine has been advocated as a therapeutic procedure. The achievement of an alkaline urine through administration of large amounts of sodium bicarbonate or sodium lactate is distinctly dangerous. Smaller amounts may be effective, but definitive data on the excretion of bicarbonate under these circumstances are lacking. Repair of sodium and potassium depletion by the methods outlined above should favor excretion of an alkaline urine.

Another suggested approach to this problem has been to administer a carbonic anhydrase inhibitor, acetazolamide (Diamox), since inhibition of carbonic anhydrase in the renal tubular cells limits the rate of secretion of hydrogen ions into the urine, thereby increasing bicarbonate excretion and favoring an alkaline urine. To the author's knowledge, this agent has not been fully evaluated in *clinical salicylism*, although

studies in the dog[20] and in normal human subjects[22] have shown that administration of the drug is accompanied by a considerable increase in the rate of excretion of salicylate.

There are several reasons which suggest that acetazolamide may not be as useful as the foregoing considerations suppose. First, by analogy with patients with other types of metabolic acidosis,[5] patients with a mixed disturbance and an acid pH may be refractory to the action of acetazolamide. Second, to the extent that such patients would respond, this would further reduce the serum bicarbonate concentration and aggravate the acidosis. In this connection it is important to note that Kaplan and del Carmen[20] found that administration of acetazolamide increased the mortality of rats given large doses of salicylate. Third, to the extent that a positive response was obtained, the increased excretion of bicarbonate would be accompanied by increases in the excretion of sodium and potassium, further adding to the problem of restitution of deficits of these ions.

These considerations do not necessarily apply to patients who present with respiratory alkalosis, since they probably would respond by forming an alkaline urine.[26] This would be desirable not only from the point of view of increasing the excretion of salicylate, but also in ameliorating the alkalosis by reduction in serum bicarbonate. Since we lack definitive clinical and chemical data on patients treated with this agent, its indiscriminate use can hardly be recommended at present.

In severe poisoning cases extracorporeal dialysis[31] may be an important therapeutic tool, particularly if the dialysis can be carried out promptly. In performing such a dialysis, removal of salicylate is of primary importance; the bath composition should be such as to avoid raising the serum bicarbonate to normal during the dialysis. Exchange transfusion[10] or peritoneal dialysis may also prove to be effective measures for the removal of salicylate, although they are undoubtedly less efficient than the artificial kidney.

Serious Complications

The treatment of serious complications of salicylate poisoning—viz., acute pulmonary edema, respiratory depression, and bleeding—is difficult.

With *acute pulmonary edema*, oxygen and aminophylline should be used; morphine probably should not be given.[27] Digitalization with a rapidly acting glycoside may also be tried. Although acute pulmonary edema may occur spontaneously during the course of salicylism, in two of the patients studied by Winters et al.[39] pulmonary edema occurred during the initial rehydration. For this reason it is probably best to exercise caution in the rate of intravenous fluid administration to such children.

Respiratory depression should be treated with some form of artificial ventilation in an atmosphere of oxygen. For this purpose a Drinker respirator or some type of positive pressure technique should be used, preferably with laboratory control of pCO_2. *Rapid falls in pCO_2 from initially high values may be attended by serious or even fatal cardiac arrhythmias.* In one patient, an infant, treated by Winters et al.[30] apparently successful pulmonary ventilation was sustained for a protracted period through the use of an infant rocking bed.

In the presence of a *bleeding* tendency due to the low values for prothrombin, intravenous vitamin K_1 oxide should be used. Bleeding due to thrombopenia should be treated with a transfusion of fresh whole blood, observing special precautions in handling of the blood to ensure the viability of the platelets. Vitamin C should also be given to patients with salicylate poisoning because of the finding of Lutwak-Mann[21] that the excretion of this substance is accelerated in experimental salicylate poisoning.

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3600 Spruce Street
Philadelphia 4, Pa.

SOLUTIONS FOR AND TECHNIQUES OF PARENTERAL, ORAL AND RECTAL ADMINISTRATION

ROBERT KAYE, M.D.

JOHN D. BRIDGERS, M.D.

DAVID M. PICOU, M.B.

The majority of significant water and electrolyte disturbances in intants and children require parenteral and particularly intravenous fluid administration. The selection of fluid to be used in an individual situation is based upon the clinician's estimate of the particular disturbance. The available solutions are numerous and may be classified according to their capacity to satisfy a variety of needs in patients with electrolyte disturbances. These may be for (1) water to repair hypohydration and to allow for insensible, sweat, gastrointestinal and renal losses; (2) calories to treat or prevent ketosis and to limit protein catabolism; (3) extracellular electrolytes to repair deficits, to support the circulation and to provide for maintenance; (4) intracellular electrolytes for deficits and maintenance. Some subjects may require whole blood for treatment of hemoglobin or blood volume deficits. Others may need plasma to correct plasma volume deficits or hypoproteinemia, calcium for treatment of hypocalcemic tetany, and so forth.

SOLUTIONS FOR FLUID THERAPY

In the present discussion no attempt will be made to describe all commercially available solutions. Solutions which have useful characteristics

From the Department of Pediatrics, University of Pennsylvania School of Medicine, and the Children's Hospital of Philadelphia.

TABLE 43. *Composition of Electrolyte and Other Solutions*

	CATIONS mEq./L.					ANIONS mEq./L.			MILLIOSMOLS/LITER (ELECTROLYTES)
	Na	K	Ca	Mg	NH_4	Cl	HCO_3 or Lactate	HPO_4	
Extracellular electrolyte:									
1. Saline:									
a. Hypertonic (3%)	513					513			1026
b. Isotonic (0.85%)	154					154			308
c. Hypotonic:									
(1/2-normal)	77					77			154
(1/3-normal)	51					51			102
(1/5-normal)	31					31			62
2. Modified saline:									
a. Ringer's	147	4	4			155			310
b. Lactated Ringer's	130	4	3			109	28		274
c. Saline—1/6 M. lactate 2:1	154					103	51		308
3. Alkalinizing:									
a. 1/6 M. Na lactate	167						167		334
b. 1/6 M. Na HCO_3	167						167		
Multiple electrolyte:									
1. Isotonic:									
a. Darrow's	122	35				104	53		314
2. Hypotonic	25	20	3			22	23	3	96
	40	35				40	20	15	150
	60	25		5		53	25	12	180
3. Special purpose:									
a. Ileostomy replacement (Lowe)	100	30				75	55		260
b. Intestinal replacement (Cooke)	138	12				100	50		300
c. Gastric replacement (Cooke)	63	17			70	150			300
4. Oral:									
8 measures/qt. Lytren	50	20	4	4		30	38	10	156

Electrolyte concentrates:	mEq./ml.
NH_4Cl	1.5
KCl	1.2
K_2PO_4	1.2
NaCl	1.25
Na lactate	1.25

Calories and water:	Gm.%	Cal./L.
1. Carbohydrate:		
a. Glucose	2.5	85
	5.0	170
	10.0	340
	20.0	680
b. Fructose	5	190
	10	380
c. Invert sugar	5	187
	10	375
2. Alcohol	5	325
3. Fat	15	1600
Plus carbohydrate	4	1600

Amino acids.....3⅛–5% solutions with carbohydrate in concentrations of 0–12.5%
2.4–5% and varying concentrations of Na, K, Cl, lactate PO_4

For increasing blood and plasma volume, hemoglobin and plasma proteins.....Blood and its derivatives
Whole blood
Packed red blood cells
Plasma
Albumin
Synthetic plasma volume expanders
Dextran
Polyvinylpyrrolidine (PVP) 6% solutions in isotonic saline or glucose

will be mentioned. Most of the electrolyte-containing solutions are available with carbohydrate in varying concentrations as a source of calories. All solutions mentioned in the text will be listed in Table 43.

Solutions Used to Provide Water and Electrolytes

The availability of the water in the various solutions is a function of its concentration of total solutes, i.e., its osmolarity. The physiologically available water contained in a given solution is that which remains over and above the amount which the retention or excretion of its content of electrolytes requires. For example, retention of 15 mEq. of sodium obligates the retention of approximately 100 ml. of water in order to maintain the normal tonicity of extracellular fluid (310 milliosmols per liter). If the amount retained were provided to the subject as isotonic saline solution, containing approximately 15 mEq. of sodium per 100 ml., no free water would be made available to the body for insensible, sweat, gastrointestinal or renal losses or to repair hypohydration. Retention of the same quantity of sodium chloride from a solution made one-half isotonic by dilution with an equal quantity of dextrose in water would make available 100 ml. of free water for other needs.

By virtue of renal concentrating mechanisms, excretion of an infused electrolyte can provide physiologically available water to the extent to which these mechanisms are operative in the individual subject. For these reasons all solutions of electrolyte concentration equal to or greater than that of extracellular fluid (iso-osmolar or hyperosmolar) must be considered deficient in physiologically available water. These considerations are part of the basis for the objection to the use of the term "physiologic" for isotonic saline and suggest the desirability, in most cases, of administering electrolytes in concentrations less than isotonic. Nevertheless situations do exist in which administration of isotonic or even hypertonic solutions of extracellular electrolytes is indicated. Isotonic solutions are useful in expanding the reduced blood or plasma volume in shock or in the burned patient. Hypertonic extracellular electrolyte solutions are of value in restoring the solute deficits of hypotonic dehydration and of hypoelectrolytemia most commonly observed following prolonged parenteral administration of solutions of insufficient electrolyte content.

Isotonic electrolyte solutions are preferred for subcutaneous administration because they obviate the shift of electrolytes from the vascular compartment which results when hypo-osmolar electrolyte solutions are introduced subcutaneously. Hypertonic solutions containing glucose when administered subcutaneously may draw significant amounts of water and electrolyte from the vascular bed. In both situations periph-

eral vascular collapse may be precipitated in patients with diminished plasma osmolarity or volume.

The carbohydrate content of parenteral solutions contributes to its initial osmolarity, but by virtue of rapid utilization the osmolar concentration of sugars may be neglected, and its accompanying water may be considered to be entirely available. This is not so when carbohydrate solutions are administered subcutaneously, in which case they exert an osmotic effect until absorbed into the blood and utilized. A 5 per cent dextrose or fructose solution is isosmolar with respect to extracellular fluid.

Another deficiency of saline solutions has received considerable emphasis. Solutions of saline contain equal quantities of sodium and chloride, while the ratio in extracellular fluid is approximately 3 parts of sodium to 2 of chloride. The chloride excess of saline solutions constitutes an acid load which must be excreted. As many of the situations for which parenteral fluid therapy is required are accompanied by metabolic acidosis, use of unmodified sodium chloride solutions is indeed unphysiologic. Its relative chloride excess is useful in the treatment of deficiency of this anion present in metabolic alkalosis resulting from loss of gastric hydrochloric acid.

Solutions have been devised which correct this imbalance. This has been accomplished by substitution of sodium lactate for some of the sodium chloride as in lactated Ringer's solution. A mixture of 2 parts of sodium chloride to one of seventh-molar* sodium lactate establishes the more physiologic 3:2 ratio of sodium to chloride.[2] This solution may be considered alkalinizing by virtue of its content of bicarbonate percursors, which is approximately twice that of extracellular fluid. This is advantageous in patients with the bicarbonate deficit of metabolic acidosis. Because solutions with 3:2 sodium:chloride ratio are well tolerated by patients with intact homeostatic mechanisms, they are routinely used in some clinics to provide extracellular electrolytes. Such solutions are contraindicated in patients with the bicarbonate excess and chloride deficit of metabolic alkalosis.

Some of the excess lactate may be replaced by phosphate, producing a balance between sodium, chloride and lactate which more closely resembles that of normal extracellular fluid. Although the addition of phosphate to parenteral solutions may be desirable for the above-mentioned reason, the presence in bone of a large body reservoir of this substance makes this a relatively unimportant matter compared to the necessity for inclusion of the extracellular electrolytes sodium and chloride, for which there are no reserve stores. Talbot has pointed out

* The more widely used sixth-molar sodium lactate solution may be interchanged here.

an additional advantage of including phosphate in parenteral solutions in that the portion excreted in the urine adds to its buffering capacity.[9]

The use of sodium bicarbonate solutions may be indicated occasionally when profound and life-threatening acidosis exists. In general, the conversion of lactate to bicarbonate can be depended upon. It is doubtful whether the slight impairments in lactate metabolism demonstrable in severe liver disease, anoxia and thiamine deficiency ever constitute contraindications to the treatment of metabolic acidosis with lactate solutions.

Thus far the discussion of parenteral solutions has been limited to consideration of their content of water, carbohydrate and the extracellular electrolytes sodium, chloride and bicarbonate. Phosphate, although it is the major intracellular anion, has been considered chiefly from the standpoint of its use in the formulation of a solution offering a more physiologic balance between the principal extracellular electrolytes.

The demonstration by Darrow[4] of the considerable magnitude of the deficits of the major intracellular cation potassium, in infants with diarrheal dehydration, and the ability of parenterally administered potassium to correct them, has led to its inclusion in a variety of parenteral solutions. The amount of potassium (5 mEq. per liter) contained in Ringer's solution which had been in use before Darrow's demonstration is insufficient for the repair of cellular deficits. More concentrated potassium-containing solutions have been developed which make possible the provision of maintenance requirements as well as the repair of deficits. The concentrations of potassium contained in the solutions in widespread use have been selected on the basis of several important criteria: total osmolarity, the requirements and tolerances for all its constituent electrolytes, and safety in terms of avoidance of the cardiac toxicity of excessive concentrations of serum potassium.

Solutions of this type are commercially available and contain 20 to 35 mEq. per liter of potassium with 25 and 40 mEq. of sodium respectively. The latter solution is generally preferable for use in patients with significant deficits of both cations. Both solutions may be satisfactorily used in patients requiring maintenance therapy only.

In the absence of definite evidence of hypokalemia, potassium-containing solutions should not be administered to subjects with impaired cardiorenal function caused by intrinsic disorders of these organs or by temporary impairment of their functioning secondary to shock, dehydration or adrenal cortical insufficiency. It is good policy to establish urinary output by administration of saline or saline-lactate mixtures prior to administration of potassium.

Special solutions have been devised which are of particular use in certain potential or existing electrolyte imbalances. For example, Lowe[8]

has devised a solution for the replacement of acute losses from ileostomy drainage. Its composition is given below and provides sodium in higher concentration than that of most other multiple electrolyte solutions (solutions containing both intracellular and extracellular electrolytes).

Severe vomiting of gastric origin leads to a proportionately greater loss of chloride than of sodium ion as well as significant deficits of potassium. Cooke has safely given a solution which provides a relative excess of chloride as the ammonium salt as well as sodium and potassium.[3] In view of the potential toxicity of ammonium solutions, some clinicians prefer to rely on sodium chloride solutions to provide the required chloride excess in this situation.

Certain commercially available solutions contain magnesium and calcium. Clear indications for their routine use have not been established, although it is the practice in many clinics to add 5 to 10 ml. of 10 per cent calcium gluconate daily to the intravenous infusions of patients recovering from diarrheal dehydration and of those receiving prolonged courses of parenteral fluids.

In addition to the solutions described above, concentrated solutions of the chlorides of ammonium, sodium and potassium are available, as well as sodium lactate and bicarbonate, potassium phosphate and glucose. These solutions are useful at times in planning therapy for a patient with needs which are not well met by any of the solutions which the physician has at hand.

A multiple electrolyte solution for oral use is commercially available (Lytren—Mead Johnson). It contains sodium, potassium, calcium, magnesium, chloride, lactate, citrate, sulfate and phosphate in an ionic strength approximately half the tonicity of extracellular fluid (osmolarity is 156 milliosmols per liter). This preparation has a place in the treatment of the early stages of diarrhea to provide replacement for increased losses of water and electrolyte. It is also useful in supplementing oral water and electrolyte intake in the recovery phase of patients with electrolyte disturbances. It must be prescribed with caution and with clear limitations as to the amounts to be administered. Excessive intakes, particularly in the face of the diminished urine output of dehydration, may result in the development of significant degrees of hypertonicity. It is safer to administer this material in half of the standard concentration (four rather than eight measures per liter).

Solutions Administered for the Purpose of Providing Calories and Water

Carbohydrate solutions are chiefly relied upon as a source of parenteral calories and water. Most widely used are 5 or 10 per cent solutions of glucose, fructose and invert sugar (equal parts of glucose and fructose). At rates of administration which are within the capacity of the infant for

complete utilization, there does not appear to be any advantage of one over the other. When this rate is exceeded, fructose utilization exceeds that of glucose, but results in a significant accumulation of lactic and pyruvic acids and the development of metabolic acidosis.[6]

Fructose may offer advantages over glucose in certain situations in which glucose utilization may be impaired: the initial hours of treatment of diabetic acidosis, febrile illness, the early postoperative period, severe hepatic insufficiency, after fasting and in the acidotic state.

Preparations of fat emulsions for intravenous use are extremely potent from a caloric standpoint. Lipomul (Upjohn), a 15 per cent fat emulsion in 4 per cent glucose, provides 1600 calories per liter compared to approximately 400 calories in an equal volume of 10 per cent glucose or fructose. The rate recommended for intravenous administration of 15 per cent fat emulsions to infants and children is 5.0 ml. per kilogram per hour for 6 hours. This quantity provides 48 calories per kilogram. Febrile reactions are the chief toxic effect encountered in daily infusion over a period of a few days to a week. Prolonged infusion for several weeks has resulted in some instances of fatal hemolytic reactions. For these reasons the preparations have thus far been cleared for investigational use only. In some instances in which caloric deprivation has been sufficiently prolonged as to threaten life we have felt that the use of intravenous fat has been chiefly instrumental in initiating recovery.[7]

Alcohol can be added to solutions containing glucose or fructose. The additional calories provided by 5 per cent alcohol solutions administered at the recommended rate of 40 ml. per kilogram per 24 hours (13 calories per kilogram) are not sufficient to argue strongly for its use in pediatric patients.

Solutions Used to Provide Nitrogen

A variety of preparations of hydrolyzed proteins are available for intravenous administration. These are prepared from high quality protein sources such as casein, fibrin or bovine plasma by enzymatic or acid hydrolysis. The solutions as prepared contain amino acids and polypeptides. Calories to promote utilization of the administered nitrogen are supplied by including carbohydrate and, in some preparations, alcohol as well. When administered with adequate calories in amounts sufficient to provide the equivalent of 1 to 2 gm. of protein per kilogram per day, these solutions will minimize protein catabolism and contribute to the repair of deficits.[8] Amino acid solutions are contraindicated in patients with severe renal or hepatic impairment, and strict aseptic technique must be used in order to avoid bacterial contamination.

Solutions Used to Increase Blood Volume, Plasma Protein and Hemoglobin

Although the chief uses of plasma and human serum albumin solutions are to repair plasma protein and plasma volume deficits, they may be used to provide metabolic nitrogen as well. Limitations on the quantity that can be safely administered because of the expansion of blood volume produced by these substances, as well as the expense, make their use impractical for this purpose. Pooled plasma, but not albumin, has the additional disadvantage of transmission of serum hepatitis. This

TABLE 44. *Classification of Solutions*

I. THOSE PROVIDING CHIEFLY EXTRACELLULAR ELECTROLYTE
- A. Saline solutions
  1. Hypertonic
  2. Isotonic
  3. Hypotonic
- B. Modified extracellular electrolyte solutions
  1. Ringer's solution
  2. Lactated Ringer's solution
  3. 2:1 saline — 1/6M lactate mixtures
- C. Alkalinizing solutions
  1. 1/6M sodium lactate
  2. 1/6M sodium bicarbonate

II. THOSE PROVIDING SIGNIFICANT AMOUNTS OF EXTRACELLULAR AND INTRACELLULAR ELECTROLYTES (MULTIPLE ELECTROLYTE SOLUTIONS)
- A. Isotonic multiple electrolyte solutions
  1. Darrow's solution
- B. Hypotonic multiple electrolyte solutions
- C. Special purpose multiple electrolyte solutions
  1. Ileostomy replacement solution
  2. Intestinal replacement solution
  3. Gastric replacement solution
- D. Multiple electrolyte solutions for oral use

III. ELECTROLYTE CONCENTRATES

IV. SOLUTIONS PROVIDING CALORIES AND WATER
- A. Carbohydrate solutions
  1. Glucose
  2. Fructose
  3. Invert sugar
- B. Alcohol
- C. Fat

V. SOLUTIONS PROVIDING AMINO ACIDS

VI. SOLUTIONS FOR INCREASING BLOOD AND PLASMA VOLUME, HEMOGLOBIN AND PLASMA PROTEINS
- A. Blood and its derivatives
  1. Whole blood
  2. Packed red blood cells
  3. Plasma
  4. Albumin
- B. Synthetic plasma volume expanders
  1. Dextran
  2. Polyvinylpyrrolidine (PVP)

hazard can be minimized by prolonged storage at room temperature or by use of plasma from individual bleedings.

Ebert[5] has emphasized that minor decreases in blood volume up to 20 per cent may be well tolerated and unaccompanied by symptoms. Losses up to 30 to 40 per cent of blood volume are associated with signs of clinical shock. Assuming average blood volume for infants and older children to equal 60 and 80 ml. per kilogram respectively, one can calculate reasonable dosages of blood for shock secondary to hemorrhage and of plasma for the treatment of shock from other causes.

If blood volume is normal and transfusions are used to correct anemia or hypoproteinemia, it is important not to expand blood volume dangerously. Transfusions should not exceed 20 per cent of the estimated normal blood volume, i.e., not above 12 ml. per kilogram for infants or 16 ml. for older children. Similar considerations may be applied to the use of packed red blood cells for treatment of anemia.

Plasma Substitutes

These substances, because of their large molecular size, diffuse slowly from the vascular bed and thereby exert an osmotic effect which expands plasma volume. They can be produced cheaply and in large quantities. Most commonly used are 6 per cent solutions of dextran, a polymer of glucose of high molecular weight, and polyvinylpyrrolidine (PVP). The greatest effect of the substances lasts 6 to 12 hours. Although they have been used to increase plasma volume in shock, burns and in nephrosis, their chief value appears to lie in the treatment of mass casualties when supplies of plasma, albumin and blood may be inadequate.[9]

FLUID THERAPY TECHNIQUES

Use of the Alimentary Canal

GAVAGE. Soft polyethylene tubing is less irritating to mucosal surfaces than a rubber catheter, and may be left in place over several feedings without undue discomfort. If tips are roughened, they should be coated with paraffin to safeguard against gastric perforation.

Installation may require restraint. A length of tubing measured from the bridge of the nose to the xiphoid should reach the stomach. The tube should be moistened and carefully advanced through the nostril. Introduction into the larynx can be avoided by acutely flexing the patient's neck as the tube is passed through the oropharynx. Positioning in the stomach can be confirmed by aspiration of the gastric contents or by auscultation for "bubbling" over the left upper abdomen as a small quantity of air is injected into the tube. The tube should be fixed in place by taping above the upper lip and across the cheek in order to prevent dislodgment by "rooting."

The barrel of a large syringe serves as an open container from which

solutions can be gravity-fed into the tube. Connection of the tube to a standard drip-chamber allows adequate regulation of flow when continuous or periodic drip feeding is necessary. Long-term use of a nasogastric tube may predispose to moniliasis, but such infections can usually be controlled with antimycotic drugs.

Rectal Infusion. The administration of supplemental fluids and electrolytes by rectum is a method more honored by time than by success; however, this procedure can be of benefit at times in home care. Large amounts injected into the rectum are seldom retained or absorbed by small children, so that infusions should be limited to 50 to 75 cc. every several hours.

Parenteral Therapy Techniques

The traditional routes of parenteral fluid administration include intravenous, subcutaneous, intraosseous and intraperitoneal infusions. The intravenous route is the most efficacious, and accommodates a large spectrum of solutions. Intraosseous and intraperitoneal infusions have been advocated as emergency procedures when venoclysis is difficult, but pose serious risks of infection. Presently available intravenous techniques make resort to these measures rarely justifiable.

General Considerations in Intravenous Techniques. Written orders should be explicit as to the type of solution and the rate of administration. Rate should be specified in drops per minute, by which the flow is adjusted, as well as in cubic centimeters per hour, by which progress is gauged. It is advisable to have available for ready reference a flow-rate table equating cubic centimeters per hour to drops per minute. A rough estimate of flow may be derived from the formula:

$$\text{Ml./hr.} = \text{drops/min.} \times 3.$$

A running and cumulative record of the amount and type of parenteral fluid intake should be carefully maintained at the bedside. The simplicity of such a chart should allow its maintenance by the various nurses sharing in the care of the patient. To avoid serious consequences of accidental rapid infusion, it is well to limit the volume of a single bottle of fluid to no more than one quarter of the daily requirement.

Adequate restraint is usually necessary for the introduction and maintenance in place of the intravenous needle or cannula. An assistant to provide this during insertion is a necessary adjunct to the practitioner's manual skill in such pediatric procedures which require precision. Infants and small children should be "mummified" in a sheet so that thrashing does not divert the assistant from the main task of immobilizing the member upon which the physician is engaged. Movement of an extremity can best be limited by taping to a padded board. The board can be made easily from a thin splinting board, padded with ½-inch foam rubber sheeting, and covered with knitted stockinet. A board of sufficient size should be selected to allow immobilization of all intrinsic joints of the limb used, i.e., the knee, ankle and foot or the elbow,

wrist and hand. Strapping should be done with wide adhesive tape, since narrow bands tend to be more constricting to the circulation. The board can later be pinned to the bedding for continuing restraint. Periodic checking of the snugness of the strapping is a necessary precaution against undue pressure over bony prominences causing necrosis by compromising skin circulation.

The most accessible veins in the young infant for fluid therapy are in the scalp, with the superficial veins on the volar surface of the wrist the next best site. In the young child the scalp veins become inaccessible, whereas the veins around the wrist and ankle become more prominent. In the later preschool years the antecubital veins and the larger radicles around the ankles and over the back of the hands can be utilized much as in the adult. When using the veins of an extremity, placing a tourniquet proximal to the site will facilitate locating and cannulating the vessel. Adequate preparation must include shaving of hair as well as the usual thorough antiseptic cleansing.

VENOCLYSIS USING SMALL VEIN. A 22- or 23-gauge needle of appropriate length is attached to a tuberculin syringe containing isotonic saline solution. The skin over the area should be drawn taut to anchor the vein and to prevent the skin from "pushing-up" ahead of the needle. The needle is inserted, bevel up, through the skin in line with the vein, and advanced slowly along the course of the vessel. Aspiration on the syringe frequently collapses a thin-walled vein, so that competence of the venipuncture cannot always be judged in this manner. Instead, when it is felt that the needle is in the lumen of the vein, a small amount of saline should be injected. Flow will be free with a properly placed insertion, whereas with the needle outside the vein the injection will produce a small subcutaneous bleb which can easily be dissipated by finger-tip massage. Once the vein has been entered, care is needed to avoid penetrating the opposite wall. If the needle is threaded farther into the vessel, saline should be injected as the needle is advanced in order to "balloon" the vein. The needle hub should be securely taped to the skin before attempting to disengage the syringe in order to connect the tubing from the drip-chamber. A loose loop of tubing several inches from the adapter should also be taped to the skin, leaving slight slack between the loop and the hub so that tension on the tubing due to movement is not applied directly to the needle.

This arrangement is cumbersome at best, and the success of infusion through small veins has been much enhanced by use of the scalp-vein needle designed by Gardner and Murphy. The device consists in interposing a length of polyethylene tubing between the needle shaft and hub. This permits taping the shaft flat against the skin, and the lightness and flexibility of the plastic tubing produce much less torsion on the needle point. Such a device can be prepared from a standard needle; however, they are now available commercially.

Its use is demonstrated in Figures 42 and 43. The needle is grasped by a small hemostat and inserted as in the routine procedure described above. When the vein is entered, blood should ascend into the plastic tubing by capillary action which can be augmented by aspiration on an attached syringe. The needle can be held in place by finger pressure while tape is applied over the entire needle shaft. This technique is particularly effective in the use of scalp veins, where continuous restraint of the head is undesirable. A satisfactory set-up will frequently operate successfully for several days.

Fig. 42.

Fig. 43.

VENOUS CANNULATION. When the need for fluid administration is urgent and superficial veins are inaccessible, cannulation of a vein with polyethylene tubing is indicated. Any available limb vein may be used; however, the internal malleolar vein is most suitable. It can sometimes be visualized with the aid of a tourniquet, although the anatomy of the area is sufficiently consistent to allow a "blind" approach. This is frequently necessary when peripheral vascular collapse renders the

procedure necessary. The tubing is available commercially in individual sterile packages of short lengths of various calibers. Because of the frequent emergency need, standard sterile packs of the required instruments and material should be available at all times.

With the extremity immobilized, the procedure should be carried out with aseptic technique. Before starting the "cut-down" proper, the tubing should be prepared by beveling one end, fixing an adapter or standard needle to the other end, and filling the tubing with isotonic saline solution.

A local anesthetic (1 per cent procaine) should be injected intracutaneously and subcutaneously in the area anterior to the internal malleolus. A ½-inch transverse incision is placed adjacent to the center of the malleolar eminence midway between the malleolus and the anterior aspect of the ankle. The skin edges and subcutaneous tissues are spread with the hemostat tips. At times the vein can be seen at the base of the incision. If not, the vein can usually be delivered into the wound by exploration with a small hook without further extension of the incision. If the vein is blanched by the pressure of being lifted, it can be differentiated from other structures by lowering it back into its anatomic position, when it should assume its usual bluish color. Two ligatures are passed below the vessel, and the lower ligature is tied as distally as possible. With this ligature as a retractor, the vein is raised, and a small transverse incision is placed above the level of ligation. The beveled tubing is then inserted into the vein for several centimeters until blood backs into the tubing, indicating that the catheter lies in the lumen and not between layers of the vein wall. The second suture is then tied above the incision, fixing the catheter within the vein. The skin edges are sutured around the catheter, and a sterile dressing is applied.

If it is desirable to discontinue fluid administration temporarily, the polyethylene tubing can be left in place and sealed with an obturator after flushing with saline and a weak heparin solution. The likelihood of phlebitis is fairly great after several days, and its occurrence is an indication for removal of the catheter. The vein ligatures permit withdrawal of the tubing without disrupting the skin incision to secure hemostasis.

Subcutaneous Infusion. Hypodermoclysis is the simplest form of parenteral fluid therapy from the standpoint of technique. However, in states of shock in which peripheral veins are collapsed and direct cannulation may be impossible, fluids injected subcutaneously may be poorly absorbed. The dangers of administering hypertonic or hypotonic fluids subcutaneously have been described above. The chief function of this mode of parenteral therapy is the administration of small amounts of supplemental fluid.

The site for subcutaneous injection is chosen for its ability to accommodate the fluid mass. The loose skin of the lower axillae, upper back, lower abdomen and thighs makes these areas suitable. The lateral aspects of the thighs are most commonly used for continuous infusions in older children. By utilizing a Y-tube from a gravity-drip apparatus a needle can be placed in each leg and the sides used alternately to prevent overdistention in the individual site. In infants it is most feasible to utilize the area just below both scapulae for periodic small injections. Up to 50 ml. can be administered at one time.

The area should be prepared with rigid aseptic precautions to minimize the hazard of infection. A fold of skin is raised between the fingers with a long 20-gauge needle inserted low in the fold parallel to the body surface to avoid injecting the underlying muscles. Fluid should be introduced as the needle is advanced. Pallor developing in the region of the needle point during injection indicates excessive interstitial pressure,

and the needle should be partially withdrawn and redirected toward another portion of the area. Gentle massage tends to diffuse the injected mass. In continuous infusion the hub of the indwelling needle should be taped firmly to the skin and the child sufficiently restrained to ensure immobilization of the infusion site. After discontinuing the procedure the needle wounds should be protected with a sterile dressing until thoroughly sealed over.

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1740 Bainbridge Street
Philadelphia 46, Pennsylvania

BEDSIDE LABORATORY TECHNIQUES

FRANK A. OSKI, M.D.

It is axiomatic that the sickest children are seen at night. The physician is constantly confronted with infants needing a prompt diagnosis so that rational therapy may be instituted. Often these patients are hospitalized long after the last technician has gone home and the flame in the photometer has gone out. It is no longer necessary for judgments pertaining to metabolic derangements to be made on the basis of clinical acumen alone. In recent years techniques have been perfected that enable the resourceful physician to make accurate determinations of serum chloride, total base, bicarbonate, sodium potassium and blood urea nitrogen at the bedside in a matter of moments. In addition to these electrolyte determinations, the presence of salicylates in the urine and the blood level of acetone can also be quickly assessed.

At present a compact bedside laboratory is commercially available.* The kit contains equipment and reagents necessary to perform serum chloride, bicarbonate, total base, sodium, and blood urea nitrogen determinations. The techniques outlined in the pamphlet accompanying the kit were perfected by Dr. Belden H. Scribner. The methods are straightforward, accurate and facile. For the "do-it-yourself" advocates, Dr. Scribner has published a series of articles[3-6] clearly describing how one may assemble his own kit and perform the above-mentioned determinations with rapidity. With little time and effort plus a modest financial outlay you can easily become "the first one on your block" to own and operate a portable electrolyte kit, thus saving your patients large laboratory fees and ensuring prompt and relatively accurate correction of metabolic disturbances.

A simple, rapid method for determination of *serum potassium levels* has been perfected by Keitel and Keitel.[2] It is a turbidometric deter-

From the Department of Pediatrics, Hospital of the University of Pennsylvania, Philadelphia.

* The Rochester Products Company—Rochester Bedside Lab.

mination based on the precipitation of potassium sodium cobaltinitrate. The following materials are required:

1. Two Sahli hemoglobin pipets
2. Two standard microscopic culture slides
3. One rubber-tipped glass stirring rod with a very thin tip
4. One clinical centrifuge
5. One 6 by 6 inch sheet of very black paper
6. One standard potassium solution containing potassium chloride, 3 mEq. per liter (equals 0.224 gm. per liter), and sodium chloride, 140 mm. per liter (equals 8.12 gm. per liter)
7. One standard potassium chloride solution containing potassium chloride, 5 mEq. per liter (equals 0.373 gm. per liter), and sodium chloride, 140 mm. per liter
8. 15% sodium cobaltinitrite ($Na_3CO\ (NO_2)_6$) (Baker's), chemically pure.

The following steps are performed:

1. Centrifuge a small sample of unhemolyzed blood for 2 to 10 minutes.
2. Draw off 2 samples of cell-free serum into an ordinary hemoglobin pipet to the 0.02-cc. mark and then transfer to the 2 wells of one of the slides.
3. Place 0.02-cc. aliquots of the 3- and 5-mEq. standard potassium chloride solutions on the 2 wells of the second slide.
4. Now add 0.01 cc. of the sodium cobaltinitrite reagent to each specimen in the following order:
   a. First unknown
   b. 3 mEq. standard
   c. 5 mEq. standard
   d. Second unknown.

If this order is followed, time is eliminated as a factor in speed of occurrence of the precipitation in the unknown as compared to the standards.

5. Each sample is now mixed in a rapid circular motion for five seconds. Care should be taken in wiping the rod clean between stirring operations.
6. When the even mixing is complete, the slides should be placed on the black paper and the intensities of the various precipitates compared. It has been found that the precipitates are best seen when a bright light is directed across the slide.

The 5 mEq. standard should develop a diffuse, whitish-yellow precipitate within 10 seconds. The 3 mEq. standard remains clear for approximately 20 seconds and then slowly develops a faint white precipitate around the periphery. The unknowns are now compared with the standard solutions, and an estimate of serum potassium concentration is established. The readings can usually be made within 30 seconds and must be made within 5 minutes.

When the unknown serum contains more than 5 mEq. of potassium, the potassium concentration can be approximated by diluting the unknown with an equal part of isotonic sodium chloride solution and using 0.02 cc. of this diluted specimen in your test. If the unknown contains 6 mEq., it will match the precipitate in the 3 mEq. standard; if the potassium concentration should unfortunately be as high as 10 mEq. per liter, it will match the precipitate in the 5 mEq. standard.

Keitel and Keitel state the following precautions:

a. The slides should be kept scrupulously clean. Abrasions on the slide will prevent an evenly distributed precipitate from forming.

b. Do not attempt to interpret a slide if only a localized precipitate is present.

c. Contamination of serum with either red or white cells will give falsely high values.

d. Grossly lipemic serum is unsatisfactory for potassium determinations with this rapid method.

In addition to these simple electrolyte determinations, a rapid method for determining the *blood acetone level* is available which serves as a valuable guide to insulin therapy in patients in diabetic ketosis and coma.

The test is based on the nitroprusside reaction for acetone and is performed with commercially available test tablets.* The color of the nitroprusside reaction is given by the acetone in solution as well as the acetoacetic acid.

A positive diagnosis of diabetic coma can be made in a matter of a few minutes by finding 4+ glycosuria and 4+ ketonemia. Duncan[1] states that the blood sugar level is not as reliable a guide to therapy during the first six hours of treatment as is the degree of ketonemia.

To perform the blood acetone determination, take a small amount of oxalated plasma and test it with the nitroprusside reagent and compare the result with the color scale. The test is interpreted as showing 1+ to 4+ blood acetone.

If the initial sample gives a 4+ reading, serial dilutions are then performed as a guide to initial insulin dosage. From the sample of plasma, two drops are taken and mixed with two drops of water, and one drop is tested. If this sample of 50 per cent plasma reads 4+, then 2 drops of it are mixed with an equal amount of water, and again 1 drop is tested. If this second dilution, now containing 25 per cent plasma, should read 4+, then a third dilution is performed.

For children under 12 years of age Duncan recommends giving 25 units of regular insulin immediately for each 4+ reading in the plasma and its serial dilutions (e.g., if plasma and all 3 dilutions are 4+, give 100 units of insulin). One third of the dose is given intravenously and the remainder subcutaneously.

The degree of ketonemia is then checked periodically, and as soon as the undiluted plasma gives a reaction of a lesser magnitude than 4+ ketonemia the amounts of insulin are sharply reduced.

This method may be used at the bedside even without centrifugation. Oxalated blood may be allowed to stand for a few moments until enough sedimentation has occurred to test one drop of serum. Duncan points out that contamination of the serum with some cells does not interfere with the reading of the test to a degree which would prevent recognizing a 4+ reaction.

Plasma may also be obtained rapidly by covering the end of a pipet with cotton twisted about the tip. Lower the tip into the blood sample and draw blood up into the pipet. After removing the cotton a drop of plasma may be expressed from the tube onto the reagent.

The nitroprusside reagent used on the acetone determination is also used for the *determination of salicylates.* When salicylate poisoning is suspected, the urine may be tested for its presence.[7] If a color reaction occurs with a drop of urine on the reagent, you may be dealing with keturia or salicylism. The urine is then boiled, and any color due to

* Acetest reagent tablets are available from Ames Co., Inc., Elkhart, Ind.

diacetic acid will disappear because the ketones are volatile substances. If the color persists, it is a strong indication that large amounts of salicylates have been ingested.

DISCUSSION AND SUMMARY

Rapid, simple methods are available for the determination of serum chloride, bicarbonate, total base, blood urea nitrogen, sodium, potassium, acetone, and urinary salicylate. The methods for chloride, bicarbonate, total base, and blood urea nitrogen in our hands agree within about 10 per cent with our chemical laboratory determinations. When more frequent use of these tests is made, accuracy is said to approach 1 per cent. Accuracy of the potassium method was limited to approximately 20 per cent, and acetone and salicylate are crude qualitative tests. Ordinarily, accuracy in these tests is sufficient for first approximation for therapy when other tests are not available. These bedside methods are not used in our hospital because of 24-hour availability of the chemical laboratory. Fellow interns who have frequently used the tests, however, are impressed with their usefulness in starting treatment early.

In addition to serum tests discussed here, frequent use of urinalysis, especially with regard to pH and specific gravity, allows the physician to make judicious inferences about the state of the child's serum chemistries.

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3600 Spruce Street
Philadelphia 4, Pennsylvania

BLOOD-DRAWING TECHNIQUES

WILLIAM J. MELLMAN, M.D.

WOLFGANG ANKE, M.D.

> Here lies old Joe
> He should have lived long time ago
> When folks didn' unnerstand chemistry quite so well.
> —*Exsanguination Blues.*[9]

Bloodletting as a science was practiced with proficiency, according to available woodcuts, when barbers were surgeons. None of the old pictures, however, show much in the way of drawing blood from children, and little progress was made in blood drawing from small children until the early part of the present century. Actually, there was little necessity for "bleeding" infants. Blood was taken usually only to cure plethora, and blood letting, when performed in children, almost invariably resulted in shock and death.

With the advent of chemical studies of the blood which could be interpreted and used to help in the care of small children, new techniques and new instruments were developed. First attempts were made to draw blood from areas where blood collects normally, such as the sagittal sinus. Although almost anyone could "strike oil" by piercing the sagittal sinus, the occurrence of sinus thrombosis and hemorrhage deterred many from further attempts in this area. Venous blood-drawing techniques were then developed, and the value of a pediatric resident was judged by his ability to obtain blood from the smallest infant with the least possible trauma. Senior residents, the most proficient of the group, developed the dictum, "three strikes and you're out," to prevent the junior residents from unduly injuring babies. A cult of blood

From the Department of Pediatrics, University of Pennsylvania School of Medicine, and the Hospital of the University of Pennsylvania, Philadelphia.

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drawers arose, which is now in decline, for now, with the development of microchemistry techniques in the laboratory, it will soon be possible almost universally to get capillary blood in sufficient quantity for most studies to obviate many venipunctures, and capillary blood can be got with little practice.

VENOUS BLOOD

Obtaining venous blood from infants and children in sufficient amounts for standard chemical determinations is a procedure requiring skill and experience. Although various veins are available, it is well to develop facility with one or more procedures. Proper restraint, aseptic precautions, fixation of the vein, and patience are essential to bloodletting. The psychologic aspects of venipuncture[8] are related to the emotional development of the child. That pastel-colored walls, soft lights and friendly music in the bleeding room, as some have suggested, will lessen the trauma to the psyche is difficult to prove. There is little doubt, however, that the psychologic advantage of using the smallest syringe and shortest needle possible with the utmost alacrity and confidence cannot be replaced by a premedicating dose of one of the popular tranquilizing drugs.

The psychologic approach of the physician who is to get the blood, however, is better understood. It is a common experience that the man who approaches the child with confidence, and places himself in a comfortable posture, is more likely to be successful in drawing adequate blood than is the physician who approaches the patient with a fear of missing the vein. Attention to such details as obtaining sufficient sponges and alcohol, the proper size of syringe and needle, and the proper tubes in which to place the blood once obtained, will eliminate many unnecessary punctures.

A 21- or 22-gauge needle is satisfactory in most instances, while a stiff 19- or 20-gauge needle is preferable for external jugular venipuncture. For children over three or four years the antecubital or any other superficial vein can be used. In the newborn and other infants, or when superficial veins are collapsed by circulatory shock, the most commonly used veins are the femoral and external and internal jugular veins.[10] In locating a vein, spasm is often released, and the vein becomes more prominent by slapping or rubbing the skin, or applying moist heat.

The femoral vein lies just medial to the artery, which can be palpated about the midpoint of the inguinal ligament. Puncture can be best performed with the child held in a semifrog position. The index finger of the left hand (in the right-handed) is placed on the femoral pulse. The needle is directed with a firm stroke just medial to the index finger, at an obtuse angle to the femur (Fig. 44). Some prefer to direct the needle along the index finger perpendicular to the femur (Fig. 45). As with all

venipunctures, a finger or several fingers of the hand which indicated the position of the vein should grasp the syringe barrel, and the edge of the hand should rest on the patient's thigh, so that any small movements of the patient will be accompanied by movements in a similar direction of the needle. Holding the barrel of the syringe high in the air with the other hand holding the patient results in frequent failure and frustration. The hand directing the syringe is held in such a manner that one finger can exert slight backward pressure on the plunger. As the vein is entered, a small drop of blood will rise in the syringe. With the syringe still held firmly with the left hand, the right hand is carefully repositioned around the plunger, and blood is drawn steadily

Fig. 44.

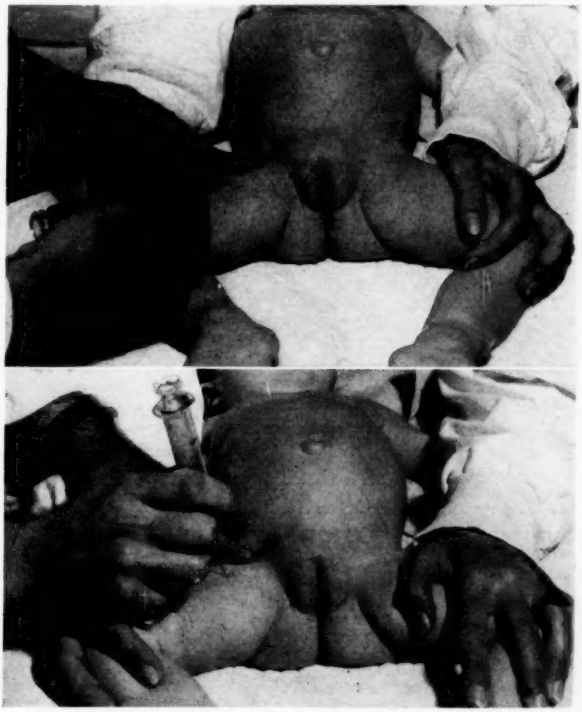

Fig. 45.

Fig. 44. Femoral venipuncture (needle inserted obliquely).
Fig. 45. Femoral venipuncture (needle inserted perpendicularly).

in until sufficient quantity is obtained. If blood is drawn too rapidly, the vein may collapse around the needle point, causing panic in the operator.

After sufficient blood has been obtained the needle is withdrawn quickly, an alcohol sponge is applied with firm pressure to the site for a minute or two, the needle is removed from the syringe, and the blood is slowly emptied into the proper receptacle. Pushing blood rapidly through the syringe, or through the needle, may cause hemolysis and ruin most chemical or immunological tests.

If blood is not obtained and the operator feels the needle tip against the femur, even though he feels that he is close to the vein, the needle should slowly be with-

drawn with one hand while the opposite hand exerts negative pressure; if no blood is obtained, the needle should be withdrawn almost to the surface of the skin, and without repiercing the skin may be redirected slightly and a second attempt made. The peritoneal cavity can be avoided by piercing the skin 3 or 4 cm. below the inguinal ligament. Utmost aseptic precautions are indicated to prevent local infections with possible extension to the hip joint or femur.[16] If arterial blood is obtained, even though this may be alarming, sufficient arterial blood should be withdrawn before removing the needle, since arterial blood is satisfactory for most chemical studies. Firm pressure over the puncture site will stop the bleeding. Arterial spasm or intra-

Fig. 46.

Fig. 47.

Fig. 46. External jugular venipuncture.
Fig. 47. Internal jugular venipuncture.

mural hematoma,[1] which occasionally occurs, must be suspected if the extremity becomes pale and pulseless. Numbness and paralysis of the extremity usually mean intramural hematoma; the ischemia of arteriospasm usually does not last long enough to produce these symptoms. Arterial spasm is attributed to a reflex mediated by the sympathetic nerves, and is usually relieved by local procaine.

The external jugular vein is easily accessible in infants unless the neck is too short or fat. The vein is superficial to the sternocleidomastoid muscle and is usually visible through the skin. The fully restrained infant is placed on his back with his head hanging over the edge of a table and turned about 45 degrees from the midline (Fig.

46). With the baby stimulated to cry, the vein becomes prominent and is seen coming from the angle of the jaw across the sternocleidomastoid muscle, dipping into deeper tissues just above the clavicle. Once the needle penetrates the skin, negative pressure should be maintained, so that air does not enter the vein. Again, the blood is withdrawn slowly. After the needle has been removed the child should be brought into an upright position while firm pressure is applied over the puncture site.

The infant is held in the same position for internal jugular as for external jugular puncture. The needle is inserted just behind the midpoint of the posterior border of the sternocleidomastoid muscle and thrust towards the suprasternal notch, keeping the needle under the muscle, but parallel to the skin surface (Fig. 47). By maintaining negative pressure in the syringe, blood appears as the vein is entered.

Jugular vein puncture is not always a benign procedure. With injudicious or unskilled probing of the deeper tissues, injuries can occur to the trachea, pleura, deep blood vessels and the vagus nerve. The positioning required is contraindicated in infants with respiratory distress and, rarely, may elicit a catastrophic reflex probably of a vagal type with temporary or permanent circulatory failure. This reflex seems to be more common in patients with anoxia, electrolyte disturbance and cardiac disease. Because of these hazards, admittedly uncommon in experienced hands, the use of the jugular veins probably should be reserved for occasions when the femoral vein is inaccessible.

The superior sagittal sinus[16] and the torcular Herophili (confluence of the sinuses)[12] are also mentioned as sources of venous blood, particularly in tiny prematures when conventional sites fail. Blood from the sagittal sinus can be obtained by inserting the needle in the midline through the posterior half of the anterior fontanel, directing the needle at an obtuse angle towards the occiput. Because the sinus is small, it can be easily perforated with resultant subdural or subarachnoid bleeding. The torcular Herophili is entered through the posterior fontanel, but is also fraught with the hazards of intracranial bleeding.

Blood can easily be obtained from small infants with a Murphy-Gardner[7] infusion set, modified by the addition of a 21-gauge needle to the free end of the tubing.[2] The polyethylene catheter is clamped with a hemostat, and the added 21-gauge needle is inserted through the rubber plug of a vacuum-containing tube. A scalp vein is entered against the blood flow with the 22- or 23-gauge needle of the Murphy-Gardner set, and the hemostat is then released. Blood will now flow by means of the vacuum into the collecting tube. This procedure has several advantages over the conventional venipuncture techniques in that it is less traumatic, minimal equipment is needed, and evenly controlled suction prevents hemolysis. Furthermore, tubes can be changed during collection should clotted or noncoagulated specimens be desired, and there is virtually no exposure to air, so that the gaseous composition of the blood remains constant during collection.

CAPILLARY BLOOD

As our basic understanding of electrolyte disturbances becomes more complex, chemical analysis of the blood is being demanded with greater regularity. Frequently, serial determinations of extracellular components are required to monitor intelligently treatment of the more profound electrolyte disturbances. Until the clinical chemist devised techniques of microanalysis, the volumes of blood needed for most studies were

often prohibitive in the pediatric age group. No longer must replenishment transfusion be a requirement of the adequate laboratory study of small ones.

The impetus for the "more studies for less blood"[14] movement dates back to 1906,[5] when a method was developed of determining blood glucose with less than 10 ml. of blood, though 100 ml. were needed before then. Natelson[15] has noted that current nomenclature divides methodology into "microtechniques" using 0.1 to 1.0 ml. of blood and "ultramicromethods" utilizing less than 0.1 ml. The latter methods require specially designed equipment not usually available to laboratories using standard macromethods. Although a discussion of methodology is beyond the scope of this paper,[11, 15, 18] it is generally agreed that the accuracy of these methods is comparable to those requiring larger amounts of blood. There is little reason why the chemistry laboratories of most children's hospitals will not ultimately study microquantities of blood exclusively.

The several millimeters of blood required for microchemical studies can be obtained by any of the methods described for venous blood. The method using an adapted Murphy-Gardner set[2] is particularly valuable for collecting small volumes where the laboratory is not equipped to work with capillary tubes. Without the use of ultramicro equipment, serum sodium, potassium, carbon dioxide and chloride can be readily determined with 2 ml. of blood.

The use of capillary blood for routine chemical determinations, particularly in pediatric practice, has multiple advantages. No longer must a team of athletic nurses be available to restrain the child while the intern searches anxiously for a vein that will give enough blood to satisfy the fancy of a laboratory technician. Compare the horror scene of the venipuncture with the picture of a doctor or technician tenderly but firmly holding the child's finger or heel, and making a quick stab with a blade certain to bring forth capillary blood. Furthermore, avoiding a phlebotomy for the removal of diagnostic blood preserves veins that may be needed for intravenous therapy. Consider, too, the difficulty, often impossibility, of gathering blood from inaccessible veins in the presence of circulatory collapse. Even in the dehydrated infant a heel puncture will usually produce sufficient blood for the required electrolyte studies. In the situation of profound contraction of the peripheral vessels, preliminary heating of the part will often produce the needed local hyperemia.

In the infant the heel is ideal for obtaining capillary blood, puncturing the plantar surface of the foot anterior and medial to the potential heel pad, areas corresponding to the course of the lateral and medial plantar arteries. The avoidance of the heel pad is a precaution against the rare development of a scar, which might be painful if it were on

a weight-bearing surface. The medial aspect of the fingers is the most satisfactory site of puncture in the older child. When all conventional sources of blood are wanting, the ear lobe may be utilized,[15] particularly in the patient with massive burns involving all extremities. The incision should be made in the bottom edge of the ear lobe, and if flow is not optimal, local dry heat may be applied.

A no. 11 Bard-Parker blade, rather than a hematologic lancet, is needed to obtain a deep enough stab for adequate capillary flow. Squeezing the finger or heel should be avoided, although massaging the extremity is permissible. The first drop of blood that appears should be wiped away with a dry sponge, since the alcohol used in sterilizing the skin may produce hemolysis. In freely bleeding wounds the blood may be noted to become progressively arterial. Generally, differences in chemical values between venous and capillary blood are of no clinical significance.[3] Singer[17] has noted that capillary blood, if obtained from an extremity previously heated to the point of hyperemia, is nearly identical to arterial blood in acid-base properties.

Capillary blood is most readily collected in ordinary Pyrex tubing with an approximate outside diameter of 2.8 mm., inside diameter of 1.5 mm., and length of 15 cm. One end of the tube is drawn to about an 0.8-mm. bore. Tubes meeting these specifications are now commercially available. The tapered tip is held horizontally or slightly downward in the drop of blood, allowing capillarity and gravity to fill the tube about two thirds. This much blood provides about 0.08 to 0.1 ml. of serum after centrifugation. Four or five such tubes contain enough blood for determining serum sodium, potassium, chloride and carbon dioxide. Some laboratories suggest heparinizing the capillaries before bleeding the patient, but this has been found unnecessary in our hands and at the Children's Hospital of Philadelphia, where this technique is practiced extensively. It is well to remember that heparin is supplied as the sodium or calcium salt, which produces some contamination of the serum. Pretreatment of the capillary tubes with silicon coverings may prevent mineral transfer from the glass to the specimen.

The use of a calibrated capillary tube of constant internal diameter has been introduced by White, Haidar and Reinhold.[19] This technique avoids the need for micropipets, since the volume of serum can be determined directly from the length of the serum column added to the reagent. A bilirubin method using such tubes has proved accurate and adaptable to a routine laboratory. Similar methods for other serum chemistries are currently being developed.

An alternate method for collecting capillary blood, developed by Lilienthal,[18] has been used extensively by another department of the authors' hospital. A 2-ml. syringe is heparinized, and a funnel-like adapter made from a hollowed-out no. 00 rubber stopper is placed on the tip. The arm or leg used for collection is heated in warm water until hyperemic, an incision is made, and the blood is allowed to drop into the rubber tip and is drawn into the syringe. One milliliter of blood can be collected in one to three minutes by this method from the finger tip or heel. We have found limited use for this method in pediatrics, particularly since the preheating required for adequate flow is not adaptable to the acutely ill or struggling child.

SUMMARY

Several methods of obtaining venous and capillary blood have been described, with emphasis on the practical problems in small infants.

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3600 Spruce Street
Philadelphia 4, Pennsylvania

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